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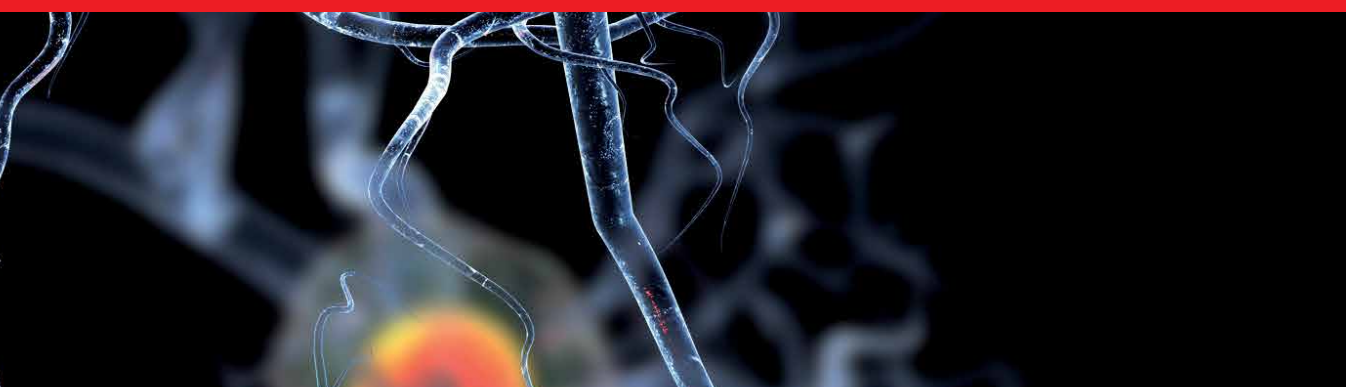
Systemic Lupus Erythematosus

Pathogenesis and Management

Edited by Sophia Lionaki



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Preface

This Edited Volume is a collection of reviewed and relevant research chapters, concerning the developments within the "Systemic Lupus Erythematosus – Pathogenesis and Management" field of study. The book includes scholarly contributions by various authors and edited by a group of experts pertinent to lupus erythematosus. Each contribution comes as a separate chapter complete in itself but directly related to the book's topics and objectives.

The book is divided into 5 sections: "Treatment", "Cardiovascular Disease", "Pathogenesis", "Neuropsychiatric Involvement" and "Fertility and Lupus".

Section "Treatment" includes chapters dealing with the topics: "Targeted Therapies for Systemic Lupus Erythematosus (SLE): A Critical Appraisal", "Recent Advances in SLE Treatment Including Biologic Therapies" and "Lupus Nephritis: Clinical Picture, Histopathological Diagnosis, and Management".

The following section, "Cardiovascular Disease" includes one chapter: "Accelerated Atherosclerosis in SLE: Mechanisms, Consequences, and Future Directions".

Section 3 called "Pathogenesis" includes chapters:"Lupus Genetics" and "Anti-Non-Bilayer Phospholipid Arrangement Antibodies Trigger an Autoimmune Disease Similar to Systemic Lupus Erythematosus in Mice".

Section 4 called "Neuropsychiatric Involvement" includes chapters: "Lupus and the Nervous System: A Neuroimmunoloigcal Update on Pathogenesis and Management of Systemic Lupus Erythematosus with Focus on Neuropsychiatric SLE" and "Literature Review on Neuropsychiatric Lupus".

Section 5 called "Fertility and Lupus" includes chapter "Fertility, Pregnancy, and Systemic Lupus Erythematosus".

The target audience comprises scholars and specialists in the field.

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Section 1

Treatment

Chapter 1

Targeted Therapies for Systemic Lupus Erythematosus (SLE): A Critical Appraisal

Georgia-Savina Moysidou and Dimitrios T. Boumpas

Abstract

Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disease characterized by a wide range of manifestations from mild to life-threatening. Prognosis has markedly improved in the last decades due to earlier diagnosis, prevention of comorbidities, and the use of more intensive treatment regimens. However, the high rates of morbidity, despite treatment, reflect the presence of numerous unmet medical needs in patients with SLE, calling for new, treat-to-target strategies. To date, only two biological agents, belimumab and recently anifrolumab, have been approved in patients with SLE with several others showing promising results. In this review, we critically review the data, with emphasis on the approved biologics.

Keywords: systemic lupus erythematosus, pathogenesis, biologic therapies, targeted therapies, B-cells

1. Introduction

Systemic lupus erythematosus (SLE) is a complex autoimmune disease with significant morbidity and mortality rates. Hydroxychloroquine remains the hallmark in the management of SLE, exerting beneficial effects not only in mild manifestations but also in serious organ involvement [1]. In 2011, belimumab, a monoclonal antibody antagonizing soluble B-lymphocyte stimulator protein (BLyS) became the first approved biologic treatment in SLE patients with active, extrarenal, seropositive disease [2]. A decade later, in 2021, the US Food and Drug Administration (FDA) approved anifrolumab, a monoclonal antibody antagonist of the type 1 interferon receptor for the treatment of adult patients with moderate to severe SLE who are receiving standard therapy [3].

Despite these advances, corticoid dependence and the high rates of relapse underscore the need for more efficient treatment strategies.

In this chapter, we will review current as well as emerging biological therapies in SLE and provide the mechanistic rationale behind their development (**Table 1**).

• SLE pathogenesis is multifactorial and elusive
• In genetically predisposed humans, epigenetic factors such as DNA methylation, environmental factors including ultraviolet light and hormonal factors, lead to loss of tolerance to self-antigens, and immune responses
• Defective clearance of apoptotic cells plays also a central role to SLE pathogenesis, leading to the accumulation of endogenous nucleic acids, stimulating Toll-like receptors (TLRs), and inducing a strong type I interferon (IFN) production
• Autoimmunity is sustained and amplified by multiple cytokines by multiple immune reactants including immune complexes and cytokines

Table 1.
Keys to SLE pathogenesis [4–7].

2. Steps to SLE pathogenesis

The pathogenesis of SLE is elusive and multifactorial. Mutations in genes related to toll-like receptors and type 1 interferon (IFN) signaling pathways and apoptotic waste clearance epigenetic factors such as DNA methylation and environmental factors including ultraviolet light, hormones, and viruses contribute to its manifestation [4]. Over 100 genetic loci identified through genome-wide association studies (GWAS) are associated with SLE [5].

Defective clearance of apoptotic cells and the accumulation of apoptotic debris play a key role in SLE pathogenesis [6], by stimulating the production of IFNa and promotion of autoimmunity due to a breakdown of self-tolerance. Neutrophil extracellular traps released by dying neutrophils during a process called NETosis may serve as well as a source of autoantigens [7]. Another key to SLE pathogenesis is Toll-like receptors (TLRs). TLRs are expressed in multiple immune cells including dendritic cells, macrophages, B and T cells are also stimulated by nucleic acids contained in apoptotic cells [4] and inducing a strong type I IFN production and plasmacytoid dendritic cells' activation.

The amplification and maintenance of autoimmunity in SLE patients are driven by multiple immune reactants including immune complexes, type I IFN, and other cytokines including B- cell activating factor (BAFF or BLyS), the target of Belimumab. Loss of T and B cell tolerance, deficient regulatory T cells (Tregs), aberrant development of B cells leading to production of autoantibodies play also a central role in SLE pathogenesis.

3. B-cell targeting treatments

B-cells are key cells in the pathogenesis of SLE, and their targeting has drawn the attention for several decades.

3.1 BAFF/BLyS inhibition

B-cell activating factor (BAFF) is a cytokine responsible for proliferation, survival, and differentiation of B lymphocytes into antibody producing

plasmocytes, playing a crucial role in the pathogenesis of SLE. The presence of anti-BAFF antibodies correlated with disease severity and the presence of IFN signature in SLE patients [8].

These findings led to further research on the use of BAFF as a therapeutic target in SLE patients.

3.2 Belimumab

Belimumab is a human monoclonal anti-BLyS antibody binding to and antagonizing soluble human BLyS and selectively reducing the numbers of subsets of CD20+ B lymphocytes [2]. It was approved by FDA after the results of BLISS-52 and BLISS-76 [2, 9], two multicenter, placebo-controlled studies. In both studies, belimumab was associated with a significantly higher SRI-4 response rate at 52 weeks and reduction of severe SLE flares with an excellent safety profile, in patients with active SLE. Patients with severe active lupus nephritis or severe central nervous system (CNS) manifestations were excluded from the study. In 2020, Belimumab proved its efficacy in patients with active lupus nephritis as an add-on to standard of care therapy, by improving rates of achievement of primary efficacy renal response and a complete renal response at week 104 [10]; these results were though significant only in the mycophenolate group and not in the cyclophosphamide or azathioprine group. Importantly, belimumab was efficient in reducing the risk of flares in patients with refractory SLE after treatment with Rituximab [11]. Belimumab has also proven its efficacy in pediatric SLE patients [12].

3.3 Other BLyS inhibitors

Atacicept is a dual APRIL/BLyS inhibitor, reducing total B cell, plasma cell, and serum immunoglobulin levels, which showed evidence of efficacy in the ADRESS IIB study, with SLE patients with moderate to high disease activity [13]; in this study, patients with severe active renal or CNS involvement were excluded.

Blisibimod is a potent and selective BAFF inhibitor composed of a tetrameric BAFF binding domain fused to a human IgG1 Fc region. Blisibimod failed to meet the SLE responder Index-6 (SRI-6) primary endpoint in the PEARL-SC phase III trial, including SLE patients with seropositive SLE and moderate to high disease activity (SELEnA-SLEdAI) score ≥ 10 despite standard-of-care medications [14]; however, it showed encouraging results in terms of successful steroid reduction, decrease of proteinuria and biomarker responses.

Tabalumab, a human IgG4 monoclonal antibody binding and neutralizing membrane and soluble BAFF versus placebo plus standard of care, failed to prove its efficacy in the ILLUMINATE-1 study, a phase III trial in patients with moderate to severe SLE [15].

3.4 B-cell depletion strategies

B cells play a fundamental role in the pathogenesis of SLE through cytokine and autoantibody production and T cell activation. Multiple B-cell depleting strategies have been studied in patients with SLE, but they are most of the times reserved for the treatment of refractory patients.

3.5 Rituximab

Rituximab is a chimeric anti-CD20 monoclonal antibody, sparing stem cells and plasma cells. Despite the crucial role of lymphocytes B in SLE, there are no large randomized controlled trials confirming its efficacy, probably due to study design problems. In the EXPLORER trial, a multicenter, double-blind, placebo-controlled trial, rituximab failed to achieve major or partial clinical responses, as assessed by the BILAG index score [16]. Rituximab was also evaluated in patients with active proliferative lupus nephritis, in the LUNAR trial [17], in association with mycophenolate mofetil; the primary end point, superior response rate in the rituximab group, was not met, but patients treated with rituximab showed higher improvement in serological activity and proteinuria than those treated with placebo. Rituximab has shown evidence of effectiveness in patients with NPSLE as induction therapy as well as in refractory cases, in case series and non-controlled studies [18], but these results need to be confirmed in larger randomized controlled trials.

3.6 Obinutuzumab

Obinutuzumab is a Type II anti-CD20 monoclonal antibody used in the treatment of B-cell malignancies [19]. In lupus-prone MRL/lpr mice, it showed superiority not only in terms of B-cell depletion but also in clinical and biological parameters such as glomerulonephritis and anti-RNA autoantibody titers [20]. These encouraging results were confirmed in a small case series of nine patients with secondary non-response to rituximab; of note one unvaccinated patient died from Covid-19 [21]. Following these data, obinutuzumab was tested in patients with proliferative lupus nephritis in association with mycophenolate mofetil and steroids, in NOBILITY, a phase 2, randomized, double-blind, placebo-controlled trial. In this study, Obinutuzumab was superior to placebo in the achievement of complete renal response at week 104 (26 (41%) vs. 14 (23%), $p = 0.026$) [22].

3.7 Ofatumumab

Ofatumumab is a human IgG1κ anti-CD20 monoclonal antibody that binds to CD20 with a higher affinity compared with rituximab, used in the treatment of chronic lymphocytic leukemia and relapsing remitting multiple sclerosis, which has been used with success in patients with RA [23]. In SLE, it has mostly been studied in patients with prior allergic reaction to rituximab with a good safety profile [24]. In a case series of four patients with refractory lupus nephritis with good clinical response but the development of adverse effects to rituximab, it led to a reduction albuminuria in all four cases [25]. One patient developed widespread urticaria and the treatment was discontinued. To date, there are no RCTs evaluating its efficacy in SLE patients.

3.8 Ocrelizumab

Ocrelizumab is a recombinant humanized anti-CD20 monoclonal antibody, with higher avidity to CD20 compared with rituximab [26]. There are two RCTs assessing its efficacy in SLE. In the BELONG trial [27], ocrelizumab was evaluated in patients with active proliferative lupus nephritis in two treatment regimens (400 and 1000 mg) in association with mycophenolate mofetil or cyclophosphamide

(eurolupus, followed by maintenance with azathioprine). The study was terminated early due to severe infections in the ocrelizumab group when combined with mycophenolate mofetil; renal response was not superior in the ocrelizumab group.

3.9 Epratuzumab

Epratuzumab is a humanized anti-CD22 antibody that preferentially modulates the exaggerated activation and proliferation of B cells in SLE patients [28]. Epratuzumab was evaluated in multiple RCTs in SLE with mixed results. In the EMBODY 1 and 2 studies, epratuzumab failed to meet the primary endpoint of response rate at week 48 according to BILAG-based Combined Lupus Assessment (BICLA) definition [29]. In the underpowered ALLEVIATE-1 and -2 studies and its extension study [29, 30], epratuzumab showed encouraging though nonstatistically significant results.

3.10 CAR-T-cells

Chimeric antigen receptor (CAR)-modified T cells are genetically engineered cells that recognize CD19 and other B-cell surface antigens, currently used in B-cell malignancies. In SLE murine models, the use of CAR-T-cells led to sustained B-cell depletion [31]. CAR-T-cells were used in a 20-year-old patient with active SLE with active class IIIa lupus nephritis with nephrotic syndrome, pericarditis, pleurisy, rash, and arthritis, non-responding to conventional immunosuppression [32]. CAR-T-cell treatment was preceded by preparatory lymphodepletion with fludarabine and cyclophosphamide. The patient achieved complete clinical and serological remission within 5 weeks without severe adverse effects.

4. Targeting long-lived plasma cells

In SLE-prone mice, long-lived plasma cells (LLPCs) are present in the spleen and bone marrow, before week 4 [33] and contribute to the production of autoantibodies before the onset of symptoms. In SLE patients, long-lived plasma cells play a crucial role not only in the pathogenesis but also in the sustainment of autoimmunity and are unresponsive to standard B-cell depletion treatment by rituximab [34]. Treatment regimens, such as the combination of rituximab and belimumab [35], work toward this direction.

4.1 Daratumumab

Daratumumab is an anti-CD38 monoclonal antibody used in the treatment of multiple myeloma as well as in the treatment of AL amyloidosis [36]. It has been successfully administrated in two patients with refractory SLE [37]; belimumab was used as maintenance therapy, and treatment response was sustained during the 12-month follow-up period. The success of daratumumab was due to its pleiotropic effect in SLE patients: it eliminates LLPCs while leading to a reduction to interferon type I activity and reduction of CD19n B-cells. This observation led to the DARALUP study, a monocenter, open-label Phase II trial for refractory SLE patients [38].

5. IFN

5.1 Rationale for INF antagonists use in SLE

Interferon is a key cytokine in the pathogenesis of SLE. Interferon (IFN) signature genes are highly expressed in the peripheral blood of SLE patients [39], and interferon-inducible gene expression is associated with disease activity and lupus nephritis [40, 41]; high levels of ultrasensible IFN-a equally seem to be related with a higher risk of relapse in patients with quiescent SLE [42]. There are multiple biological therapies targeting IFN under investigation.

5.2 Anifrolumab

Anifrolumab is a human monoclonal antibody binding the IFN-I receptor subunit 1, inhibiting IFN-I signaling. It is the second biological therapy to be approved by FDA in SLE patients following the TULIP-1 [43] and TULIP-2 trials [3]. TULIP-1 [3] was a phase 3, double-blind, RCT of adults with moderate to severe SLE despite standard-of-care treatment, where patients were randomized to receive anifrolumab in two treatment regimens or placebo; the primary endpoint of SRI-4 at week 52 was not met, but a clinical benefit was observed in the anifrolumab group in terms of steroid sparing effect, skin lesions (as assessed by Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI)) and British Isles Lupus Assessment Group–based Composite Lupus Assessment (BICLA) response. In TULIP 2 [3], patients were assigned to receive anifrolumab at 300 mg every 4 weeks or placebo; the primary endpoint of BICLA response at week 52 was achieved (47.8% in the anifrolumab group and 31.5% in the placebo group, $p = 0.001$). In a phase II trial assessing anifrolumab in association with mycophenolate mofetil and steroids, in patients with active proliferative LN [44], the primary endpoint of change in baseline 24-hour urine protein-creatinine ratio (UPCR) at week (W) 52 was not met, but there were encouraging though nonstatistically significant results in the anifrolumab group in complete renal response and corticoid sparing effect. Patients with high interferon signature genes were more likely to reach BICLA response at week 52 according to a post-hoc analysis [45]. In terms of safety, there was an increased risk of herpes zoster in the anifrolumab group [3, 44].

6. Other interferon targeting therapies

Rontalizumab is a human anti-IFN-α monoclonal antibody neutralizing all 12 IFN-α subtypes; it was assessed in SLE patients with active SLE in the ROSE trial [46], failing to reach the BILAG and SRI-4 primary and secondary endpoints at week 24. Sifalimumab is a human, IgG1 κ monoclonal antibody that neutralizes the majority of IFN-α subtypes [47]; despite the encouraging results of a phase IIb RCT, meeting the primary endpoint of SRI-4 response at week 52, the clinical trials were halted.

IFN-a kinoid is an immunotherapeutic vaccine composed of inactivated recombinant human IFN-α2b coupled to a T-helper carrier protein (keyhole limpet hemocyanin). Its aim is to induce antibodies against IFN by active immunization, thus reducing the expression of IFN-induced genes [48]. This hypothesis was confirmed

in transgenic mice expressing human IFNα2b [49]. The efficacy and safety of IFN-K were evaluated in a phase IIb, randomized, double-blind, placebo-controlled trial in adults with active systemic lupus erythematosus (SLE) and positive interferon gene signature [44]. The primary endpoints were neutralization of IFN gene signature and the BICLA at week 36 modified by mandatory corticosteroid (Cs) tapering. At week 36, 91% of the patients receiving IFN-K had neutralizing IFN antibodies and reduced IFN signature; on the contrary, the clinical primary endpoint of BICLA at week 36 was not met; of note 53% of the treated patients attained LLDAS at week 36 (vs 30% in the placebo group, $p = 0.0022$). IFN-K had also a significant corticoid sparing effect.

6.1 JAK inhibitors

Janus kinases (JAKs) and signal transducers and activators of transcription (STATs) are responsible for signal transduction of multiple cytokines and growth factors in different cell types [50]. The JAK/STAT pathway is involved in the maintenance of immune tolerance; thus, JAK/STAT dysregulation is implicated in many autoimmune diseases [51] and is an attractive treatment target. JAK inhibitors are already used in multiple rheumatic diseases such as rheumatoid arthritis (RA), ankylosing spondylitis (AS), and psoriatic arthritis (PsA). There are many in vitro and in vivo studies supporting the involvement of JAK/STAT pathway in SLE [52]. Of note, the STAT4 gene polymorphism has been associated with SLE susceptibility and renal disease [53].

Tofacitinib a JAK 1 and 3 inhibitor was evaluated in a phase I trial in SLE patients [54]. Tofacitinib was found not only to be safe but also improved cardiometabolic and immunologic parameters associated with the premature atherosclerosis and decreased IFN I gene signature.

Baricitinib is a selective JAK 1 and 2 inhibitor; in a phase II double-blind placebo-controlled RCT, it proved to be safe and effective at the dose of 4 mg in the resolution of arthritis or rash at week 24 [55]. In murine models, baricitinib ameliorated renal inflammation and led to the recovery of the expression of structural proteins in podocytes [56], indicating its potential role in the treatment of LN.

Solcitinib, a selective JAK 1 inhibitor, was evaluated in a phase II study in patients with active, extra renal SLE [57]. The study terminated due to absence of significant effect on mean IFN transcriptional biomarker expression (all panels, 50 patients). Safety data showed elevated liver enzymes in six patients (one confirmed and one suspected case of drug reaction with eosinophilia and systemic symptoms), leading to immediate dosing cessation.

Filgotinib, a Janus kinase 1 inhibitor, and lanraplenib, a spleen kinase inhibitor, have been assessed in patients with cutaneous lupus erythematosus (CLE) [58]. In a phase II trial, the primary endpoint of change from baseline in Cutaneous Lupus Erythematosus Disease Area and Severity Index Activity (CLASI-A) score at week 12 was not met; two serious adverse events (SAE) (one major cardiovascular event and hypersensitivity) were reported in the lanraplenib group and one SAE in the filgotinib group. Filgotinib and lanraplenib were also evaluated in patients with lupus membranous nephropathy [59]. The study included only nine patients, of whom only four in the filgotinib group and one in the lanraplenib group completed week 16; in the filgotinib group, all four patients had a median reduction of 50.7% in 24-hour urine protein. Further research is necessary before drawing any conclusions.

7. Other cytokine-targeted therapies

Cytokine production is distinct in patients with SLE compared with patients with other rheumatic diseases and may change during disease course and different SLE phenotypes [60]. There are multiple cytokines not only inflammatory (interferons type I and II, IL-6) but also immunomodulatory (such as IL-10 and TGF-β), implicated in the pathogenesis of the disease [61].

7.1 Targeting Interleukine-6

Interleukine 6 (IL-6) is a cytokine with pleiotropic effects in different target cells [61, 62]. In SLE patients there is an increased production and increased serum levels of IL-6 [63]. IL-6 seems to be implicated in lupus nephritis [64] and has an active role in mesangial proliferative glomerulonephritis [65]. Studies also suggest that IL-6 is implicated in an autocrine manner in maintaining B-cell hyperactivity [66].

Tocilizumab is a humanized mAb against the IL-6 receptor (IL-6R). In SLE patients, it was assessed in an open-label phase I dosage-escalation study [67] in 16 patients with mild-to-moderate disease activity in three treatment regimens: 2 mg/kg, 4 mg/kg and 8 mg/kg every 2 weeks, with a good clinical and serological response in approximately half of the patients; neutropenia occurred in all three groups with two grade III neutropenia in the 8 mg/kg group.

Sirukumab is a human, anti-IL-6 monoclonal antibody binding to IL-6 with high affinity and specificity. It has been evaluated in a phase I trial in 31 patients (23 treated with sirukumab) with cutaneous lupus erythematosus (CLE) and 15 patients with SLE (10 treated with sirukumab), with a good tolerance, but with some cases of neutro-, lympho-, or thrombocytopenia in the sirukumab group [68]. Its efficacy was also assessed in a phase II trial in patients with active proliferative lupus nephritis with persistent proteinuria despite standard of care [69], with disappointing results.

PF-04236921, a fully human immunoglobulin G2 monoclonal antibody, failed to prove its efficacy in lupus in phase II trials [70].

7.2 Interleukin 17

Interleukin 17 is a pro-inflammatory cytokine implicated in the pathogenesis of various RMDs. In SLE, the IL-17 axis seems to promote autoantibody production, immune complex deposition, and complement activation leading to tissue damage [71]. In patients with SLE, there is an increased number of Th17 cells as well as high serum levels of IL-17A, correlated with disease activity [72]. IL-17 seems to be implicated in lupus nephritis [73].

Secukinumab, a human IgG1κ monoclonal antibody, is actually assessed in a phase III trial in combination with standard of care in patients with proliferative LN [74].

7.3 Interleukin 12/23 axis

The IL23/L17 axis plays a fundamental role in multiple autoimmune diseases. In patients with active SLE, there is an upregulation of serum IL-23 and IL-23 receptor compared with healthy controls, and IL-23 seems to limit in vitro IL-2 production, leading to the promotion of autoimmunity [75]. On the other hand, IL-12 through the ILL-12-STAT4 axis is also involved in lupus pathogenesis inducing both IFN-γ and IL-21 by human CD4 + T cells [76]; of note, STAT4 is one of the most dominant risk alleles in SLE [77].

Ustekinumab is a fully human monoclonal antibody directed at the p40 subunit shared by the cytokines IL12 and IL23; in a phase 2 RCT in patients with active SLE, it resulted in higher rates of SRI-4 response in addition to standard of care at week 24 compared with placebo (p = 0•006) [78].

7.4 Low-dose IL-2

Regulatory T-cells (Tregs) under the influence of interleukin 2 (IL-2) play a crucial role in the maintenance of immune tolerance; in SLE patients there is an acquired deficiency in IL-2 leading to defects of Tregs [79]. Low-dose IL-2 corrects defects in Tregs in patients with SLE leading to restoration of immune tolerance [80]. Its potential role in clinical practice has been evaluated in two RCTs [81, 82] with a good safety profile and clinical response resulting to complete remission in seven patients with LN (53.85%, compared with 16.67% in the placebo group, p = 0.036).

7.5 T-cell strategies

In SLE, T cells are chronically active due to T-cell receptor rewiring, hypomethylation of genes related to cell activation, and mTORC1 activation [83] and are implicated in SLE pathogenesis through interaction with B-cells by enhancing the production of autoantibodies, promotion of B-cell differentiation, proliferation, and maturation [84]. Multiple T-cell strategies have already been evaluated in SLE patients.

8. CD28-CD80/86 pathway

8.1 Abatacept

Abatacept is a fusion protein of cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) with the Fc part of immunoglobulin G (IgG), selectively modulating CD80/CD86:CD28 costimulatory signal, approved for patients with RA [85]. Its results have been evaluated in multiple RCTs in SLE. Abatacept failed to prove its efficacy in a phase 2 RCT of 118 patients with SLE with non-life-threatening manifestations, but with some encouraging results in some domains such as polyarthritis [86]. Abatacept has also been evaluated in patients with proliferative LN [87], failing to meet the primary endpoint of time to confirmed complete response but was associated with greater improvements of serological activity and 20–30% greater reduction of in mean urinary protein-to-creatinine ratio compared with placebo. In the phase 2 ACCESS trial [88], patients with LN received cyclophosphamide (Eurolupus) in monotherapy or in association with abatacept; no difference was observed in the primary endpoint of frequency of complete response at week 24 (33% in the placebo arm versus 31% in the abatacept group). Abatacept has also been assessed in a phase III trial in association with MMF [89], not reaching the primary endpoint of complete renal response at W52, but with a favorable effect in proteinuria and biomarkers.

8.2 Lulizumab and theralizumab

Lulizumab pegol is an anti-CD28 domain antagonist antibody, evaluated in a Phase 2 study in patients with active SLE, not reaching the primary endpoint of the

proportion of responders using the British Isles Lupus Assessment Group (BILAG)-based Composite Lupus Assessment (BICLA) at Week 24 [90]. Theralizumab, a CD28 superagonist [91], was evaluated in a phase II study; the trial was terminated for administrative reasons.

8.3 CD40-CD40L

CD40 ligand (CD40L) is expressed on naïve and activated CD4+ T cells and platelets [92]. Its receptor, CD40, is expressed on a wide range of cells including B cells. CD40L-CD40 interaction can contribute to autoreactive B cell survival [93], making it an attractive treatment target. In a phase 1 trial [94], dapirolizumab pegol, an anti-CD40L Fab' antibody fragment conjugated to polyethylene glycol (PEG), was safe and effective in patients with active SLE. Changes in the gene expression within the plasma cell and B-cell domains were also observed. These promising results were not confirmed in the phase 2 study [95] including patients with moderately to severely active SLE. BI 655064, another humanized anti-CD40 monoclonal antibody, was evaluated in patients with proliferative lupus nephritis in combination with mycophenolate mofetil [96]; the primary endpoint of complete renal response at W52 was not met. VAY736 and CFZ533, another 2 mAb blocking the CD40 pathway, are under investigation in patients with active SLE [97]. Finally, ruplizumab, another anti-CD40 ligand mAb, was evaluated in patients with LN leading to a decrease in hematuria, proteinuria, and biomarkers [98]; the trial was prematurely terminated due to thromboembolic complications.

8.4 ICOS pathway

Targeting inducible costimulator (ICOS) is a member of the CD28 superfamily, expressed on activated T cells and binding to B7RP1, present on B cells, dendritic cells, and monocytes [99], and playing a crucial role in humoral immunity, T-cell function, and differentiation to T follicular helper cells [100]. Two ICOSL antibodies (AMG557, MEDI-570) and one ICOSL and BAFF bispecific (AMG570) have been evaluated in phase 1 trials [101–104] with a good safety profile.

9. Other molecules

9.1 Rigerimod

Rigerimod is a spliceosomal peptide recognized by lupus CD4+ T cells [105]. In a phase 2 trial, rigerimod was safe and efficient in the achievement of SRI-4 response at W12, in the group receiving 200 μg subcutaneously every 4 weeks (61.9% versus 38.6 in the placebo group ($p = 0.016$)).

9.2 Abetimus

Abetimus sodium is a tetrameric oligonucleotide conjugate reducing antidouble-stranded DNA [106]. Due to the anti-ds DNA antibodies' role in the pathogenesis of LN, abetimus was evaluated in phase 2 and phase 3 trials in a cohort of patients at high risk of nephritic flare [107, 108]. The primary endpoint of prolongation of time to renal flare was not met, despite the reduction of anti-ds DNA.

9.3 SM101

SM1O1 is a human soluble non-glycosylated version of the Fcγ receptor IIB, inhibiting the binding of immune complexes to cell-standing Fcg receptors [109] that has already been evaluated in a phase I/II trial in patients with immune thrombocytopenia with a good safety profile and clinical response [110]. In a phase 2a trial in 51 patients with SLE, it proved to be well tolerated and efficient, mostly in terms of improvement in arthritis and in skin rash (present in 75% and 50% patients, respectively) assessed by the BILAG scale [109].

10. Targeting B-cell intracellular functions

10.1 Targeting Bruton's tyrosine kinases

Bruton's tyrosine kinase (BTK) is implicated in both B-cell and Fcγ-R-mediated myeloid cell activation, playing a crucial role in B-cell survival and proliferation. BTK represents a treatment target in patients with hematological malignancies [111]. BI-BTK-1, an irreversible BTK inhibitor, ameliorated multiple pathological endpoints associated with kidney disease in two distinct murine models of spontaneous lupus nephritis [112]. Fenebrutinib (GDC-0853) a noncovalent, oral, selective BTK inhibitor was evaluated in a phase 2 trial [113], in patients with active SLE; although februtinib significantly reduced levels of CD19-positive B cells, anti- double-stranded DNA autoantibodies, and a BTK-dependent RNA signature expressed in plasmablasts compared with placebo, it failed to achieve SRI-4 response at W48. Ibrutinib, another BTK inhibitor used in B-cell malignancies, resulted in reduced levels of autoantibodies and less severe nephritis in SLE murine models [114].

10.2 Proteasome inhibitors

Long-lived plasma cells are resistant to conventional and B-cell depleting strategies and play a critical role in the maintenance of autoimmunity in patients with refractory SLE [115]. Bortezomib, a proteasome inhibitor used in multiple myeloma, has successfully been used in patients with multiple refractory autoimmune diseases including ITP [116] and warm antibody hemolytic anemia [117]. In 12 patients with refractory SLE, it not only depleted plasma cells but also ameliorated clinical manifestations [118]. These encouraging results were not confirmed in a multicenter RCT including 14 patients: there were neither serological nor statistically significant clinical effects in the bortezomib group [119]. However, in patients with LN, it seemed to reduce proteinuria, improve renal function, and decrease autoantibodies, with mild adverse events [120].

10.3 Eculizumab

Eculizumab is a fully humanized IgG2/IgG4 monoclonal antibody directed at C5, preventing the formation of the terminal complement complex, used in atypical hemolytic uraemic syndrome (aHUS) and paroxysomal nocturnal hemoglobinuria (PNH) [121]. Eculizumab has been successfully used in patients with secondary TMA due to SLE and/or APS that are non-responsive to standard of care [122].

10.4 Irbedomide

Irbedomide is a cereblon modulator targeting transcription factors Ikaros, an essential regulator of common lymphoid progenitor (CLP) stem cells and Aiolos, necessary for memory B-cell and plasma cell formation [123]. In SLE patients, irbedomide seems to modulate B-cell activation and differentiation downstream of TLR7 [123]. In a phase 2 trial, 54% of the patients receiving irbedomide at the dose of 0.45 mg reached SRI-4 at week 24, compared with 35% in the placebo group ($P = 0.01$); this difference was not statistically significant in the other irbedomide dose regimens [124].

11. Concluding remarks

Despite recent advances in the management of the majority of autoimmune diseases and the emergence of novel biological therapies, therapeutic options in SLE are rather limited. For over 50 years, and before the approval of belimumab, corticosteroids, antimalarians and traditional immunosuppressants were the only therapeutic options. This is probably due to the heterogeneity and multi-organ involvement of the disease, problems in study designs including too strict endpoints (such as no BILAG B and complete renal response), racial differences in terms of prognosis and treatment response, and the difficulty in the achievement of statistically significant difference when novel biological therapies are tested on top of the already effective, standard of care. Moreover, severely affected patients including patients with lupus nephritis and NPSLE are frequently excluded from RCTs, leading to a lack of information for these patients. Targeted treatment guided by patient's clinical and biological phenotype with the use of biomarkers and omics may result in an optimal management of the disease and achievement of remission.

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Chapter 2

Recent Advances in SLE Treatment Including Biologic Therapies

Fahidah Alenzi and David P. D'Cruz

Abstract

Systemic lupus erythematosus (SLE) is a long-term multisystem autoimmune rheumatic disease that can affect the skin, joints, kidneys, lungs, heart, and central nervous system. Clinical manifestations range from mild to severe and life-threatening diseases, which could be associated with poor outcomes, including morbidity, poor quality of life, and mortality. There is no cure for SLE, and the management is guided by organ system involvement, flare prevention, managing comorbidities, and reducing damage accumulation. Hydroxychloroquine is the most common drug that is used to control lupus disease activity. Anifrolumab is an antibody that inhibits all signaling through the type I interferon receptor and is licensed for the treatment of moderate to severe SLE. Voclosporin is a calcineurin inhibitor approved for the treatment of lupus nephritis. Belimumab as a biologic agent has been approved for the management of individuals with SLE and lupus nephritis. Despite the fact that rituximab has failed to meet its primary endpoints in clinical trials for SLE, rituximab can be used according to ACR and EULAR guidelines and is commonly used off-label for severe lupus flares. There is an unmet need for new biologic and novel therapeutic approaches in the management of SLE.

Keywords: systemic lupus erythematosus, treatment, hydroxychloroquine, biologic agent, clinical trials

1. Introduction

Systemic lupus erythematosus (SLE) is one of the most prevalent systemic autoimmune diseases caused by a dysfunctional immune system. In the SLE-affected individuals, autoantibodies are generated against tissue antigens, including nuclear, cytoplasmic, phospholipid-associated, and cell-membrane antigens—major constituents of different cell types residing in tissues and organs of the human body [1]. The binding of autoantibodies with tissue antigens generates immune complexes, which may be deposited inside tissues and organs over time. These immune complexes elicit a cascade of immune responses that result in severe inflammation and destruction of tissue architecture, leading to multiorgan dysfunction and premature mortality [2].

SLE is a long-term multisystem autoimmune rheumatic disease that can affect the skin, joints, kidneys, lungs, heart, and central nervous system. Clinical manifestations range from mild to severe and life-threatening diseases, which could

be associated with poor outcomes, including morbidity, poor quality of life, and premature mortality. There is no cure for SLE, and the management is guided by organ system involvement, flare prevention, managing comorbidities, and reducing damage accumulation. The clinical signs and course of the pathology of SLE can be altered through lifestyle alteration, such as avoiding sunlight and diet modifications. The incidence and prevalence of SLE have increased in the last few decades, possibly due to increased awareness and the ability to diagnose milder forms of SLE [3]. Studies indicate that SLE has shown strong ethnicity and gender biases. Certain ethnic groups such as those with African and Asian ancestry are more predisposed to the development of SLE. While the incidence of SLE differs between the different ethnic groups, it is interesting to note that the incidence of SLE is higher in females than in males, across all groups of ethnicities [4, 5]. Pregnant women with SLE have an increased risk of recurrent miscarriages, fetal retardation, and stillbirths especially if they are positive for antiphospholipid antibodies. The babies born to SLE mothers are at a 3% risk of having neonatal lupus especially if they are positive for anti-RO and/or anti-LA antibodies [6].

SLE is a complex disease with poorly defined etiology. Several studies have reported a strong correlation between disease incidence and certain genetic and environmental factors. About 7% of childhood-onset SLE show Mendelian inheritance and is associated with defects in genes involved in the clearance of necrotic and/or apoptotic cell debris, pathways that protect against autoimmune response against autoantigens, and those involved in autoreactive lymphocyte generation and maintenance [7–10]. Hormones are a significant underlying factor responsible for gender-biased SLE development. Specifically, estrogen and estrogen receptor signaling mediates SLE through positive regulation of CREMα transcription factor, favoring the generation of CD4+ T effector cells and double-negative T cells [11]. Several environmental factors have been associated with an increased risk of SLE. However, the time duration of exposure and dosage is not well-defined [12–14]. Particulate matter in the air, including cigarette smoke, induces oxidative stress and can damage endogenous DNA, and cellular proteins are known to trigger SLE development [15, 16]. Exogenous hormone uses, such as oral contraceptives and hormone replacement therapy, have been positively linked with SLE onset [17]. The involvement of cardiovascular disease in patients with SLE can increase the risk of mortality [18]. Renal failure and sepsis are the significant causes of mortality in patients with SLE [19]. Furthermore, autoimmune vascular injury increases the risk of atherosclerosis and coronary artery diseases in SLE patients [20].

Over the past two decades, the understanding of SLE pathogenesis and treatment has improved. Significant progress has been made in uncovering the molecular events that trigger SLE pathogenesis and exploring novel treatment options, including newly approved biologics. In this chapter, we discuss the advances in the pathogenesis of SLE and emerging treatment options.

2. Therapy with small molecules

Since SLE is an autoimmune disease affecting multiple tissues and organs, the outcome of the disease is mostly unpredictable [21, 22]. The optimum management of SLE is preventing further tissue or organ damage, preventing flares, improving the quality of patients' life, and ultimately extending the lifespan of SLE patients. However, currently available therapy is mainly focused on treating symptoms,

including flares. Antimalarials, glucocorticoids, and other immunosuppressive drugs are among the current treatments [23].

2.1 Hydroxychloroquine

Hydroxychloroquine (HCQ) belongs to the group of antimalarials. Among the oldest drugs used in SLE, chloroquine, and HCQ were introduced between 1953 and 1955 and these drugs are four aminoquinolines that are widely used to manage SLE [22, 24]. Antimalarial drugs are well-absorbed orally, and the half-life of hydroxychloroquine is around 40 or 50 days [25]. Although the mechanisms of action of antimalarial drugs in attenuating inflammation and clinical signs of SLE remain unclear, recent studies suggest a possible action on the lysosomes of the immune cells. Specifically, antimalarials increase the lysosomal vesicle pH, suppressing the antigen presentation and synthesis of inflammatory mediators, such as prostaglandins, cytokines, and chemokines [26]. One of the most beneficial effects of increasing lysosomal pH in antigen-presenting cells by antimalarials is the selective suppression of presentation of autoantigens by decreasing the binding of autoantigenic peptides to class II MHC molecules without affecting the responses against foreign antigens [26].

Similarly, chloroquine and hydroxychloroquine also inhibit Toll-like receptor (TLR) signaling in immune cells leading to reduced immune activation [27]. In addition, chloroquine treatment inhibits the production of pro-inflammatory cytokines, including TNF, IL-6, IFN-γ, IL-1β, and IL-18, in a lysosome-independent manner [28, 29]. Hydroxychloroquine reduces the serum levels of the leukocyte activation markers, including soluble CD8 and soluble IL 2 receptors [30]. Studies suggest that antimalarial agents might work as prostaglandin antagonists and inhibit the enzyme phospholipase A2 by decreasing inflammation [22, 31]. Chloroquine and hydroxychloroquine reduce dermatological manifestations, significantly protecting against skin damage by reducing the production of pro-inflammatory cytokines exposure to ultraviolet light. Moreover, chloroquine treatment also reduces matrix metalloproteinase activity and helps maintain extracellular matrix homeostasis in patients with SLE [32, 33].

HCQ is an inexpensive, well-studied, well-tolerated, and most valuable immunomodulator drug for SLE treatment. Several studies have been published on the efficacy of antimalarials in patients with SLE. Generally, HCQ is prescribed to all SLE patients with minimal contraindications or side effects, especially in patients with lupus nephritis, and is used to treat constitutional, musculoskeletal, and mucocutaneous involvement. Studies indicate that antimalarials reduce mortality in SLE patients of diverse ethnic groups [34–38]. Administration of HCQ significantly reduces the severity of SLE disease activity, which includes a reduction in active clinical involvements, serum markers, activity scores, and disease flares [39]. Randomized controlled trials (RCT) have demonstrated the benefits of HCQ in SLE, including a reduction in flares [40–42], improvement in arthralgia [41], cytokine profiles [29, 43–45], and disease severity [36, 46–49]. HCQ decreases SLE disease activity, including flares during pregnancy [39, 50]. Despite the fact that HCQ is well tolerated, it has been linked to a variety of side effects, including cardiovascular, hematological, neurological, ocular, and skin concerns [39]. HCQ reduces the recurrence of congenital heart block in anti-SSA/Ro-pregnancies in SLE mothers and can be used as a secondary preventative of fetal cardiac disease [51]. Furthermore, a combination of HCQ and mepacrine has a synergistic effect in refractory *musculocutaneous* lupus [52].

2.2 Glucocorticoids

Glucocorticoids are well known for their rapid action, potent anti-inflammatory, and immunosuppressive effects. They are part of treatment regimens for many autoimmune rheumatic diseases, including SLE. Glucocorticoids exert their action via genomic and nongenomic pathways [53]. The genomic pathway of glucocorticoids is mediated by the cytoplasmic glucocorticoid receptor, which binds to the glucocorticoids in the cytoplasm. After binding, the GC-cGR complex translocates inside the nucleus and binds to the glucocorticoid response elements present in the promoter of several target genes. The GC-GC complex decreases the transcription of inflammatory cytokines via the process known as transrepression and increases the transcription of anti-inflammatory genes by transactivation [53, 54]. The nongenomic pathway is mediated via the membrane glucocorticoid receptor, inhibition of the enzyme phospholipase A2, and alterations in the cell membranes leading to decreased lymphocyte proliferation and function [55]. While genomic mechanisms require 30 minutes for activation after administration of glucocorticoids, nongenomic mechanisms work within minutes after administration. Generally, activation of the genomic and nongenomic pathways depends on the dose of glucocorticoids. While low doses of glucocorticoids induce genomic pathways, very high doses induce nongenomic pathways of action. Specifically, the nongenomic pathway is activated at doses of more than 100 mg/day of glucocorticoids and it is sensitive to glucocorticoids, such as methylprednisolone and dexamethasone, which have five times more potent nongenomic effects than genomic ones [56]. Interestingly, the use of glucocorticoids in lupus dramatically improved the survival of patients [56, 57]. Glucocorticoids are considered primary therapy in achieving rapid control of active lupus. Studies indicate that pulse intravenous methylprednisolone reduces moderate to severe disease activity [58]. Oral prednisone at a dose of less than 30 mg/day initially and then tapering dose between 2.5 and 5 mg/day over a few weeks successfully treated SLE [59–63]. Specifically, pulses of methylprednisolone combined with other immunosuppressive drugs and HCQ were helpful in achieving rapid and prolonged lupus disease control [58, 64], resulting in the reduction of cardiovascular and global damage [58]. Glucocorticoids are the best therapeutic strategy during pregnancy in the case of lupus flares as their potent anti-inflammatory effect is not associated with teratogenicity but may increase maternal morbidity [65]. Although glucocorticoids have significantly reduced acute mortality in severe SLE, the high-dose treatment regimen for long periods has markedly increased adverse events and systemic infections, causing long-term damage. Extensive observational studies support that GC-mediated toxicity is mainly dependent on the dose and the duration of exposure [66]. It appears that doses lower than 7.5 mg/day (prednisone equivalent) may be relatively safe for long-term maintenance therapy for glucocorticoids [66–68]. In contrast, using a high dose of glucocorticoids has been associated with the development of osteonecrosis, infectious complications, and even death [69–73].

2.3 Azathioprine

Azathioprine (AZA) has been one of the oldest immunosuppressants. It is used in treating conditions, such as chronic inflammatory diseases [74], organ grafts, malignancies, and rheumatologic diseases [75]. It is a heterocyclic carbon–nitrogen aromatic compound belonging to the purine family of analogs. It is the only purine analog used in treating SLE [76]. Though its mechanism of action in

immunosuppression is controversial, AZA and its metabolite 6-mercaptopurine (6-MP) inhibit the enzymatic conversion of inosinic acid to xanthylic acid and of adenylosuccinate to adenylic acid and are known to interfere with DNA replication and de novo synthesis of nucleotides. This inhibits the replication of T-lymphocytes, as they are deprived of salvage pathways [77]. A previous study reported that AZA could induce T-cell apoptosis by inhibiting the costimulatory signaling mechanism that results in T-cell anergy, thus mitigating the effects of autoimmune cells [78]. Azathioprine is used in SLE for the management of multiple active nonrenal manifestations and renal complications, such as lupus nephritis, and is safe for use during pregnancy. AZA alone has shown encouraging results in the treatment of SLE when combined with steroids to reduce SLE mortality and morbidity [79]. Although AZA and 6-MP have been evidenced to cross the placenta [80], several studies show that when AZA is given at a lower dose, it can effectively treat SLE without affecting the fetus or creating congenital abnormalities [81].

2.4 Mycophenolate

Mycophenolate is an antiproliferative immunosuppressant drug. As an inhibitor of inosine monophosphate dehydrogenase (IMPDH) that is both uncompetitive and selective, mycophenolic acid (MPA) does not incorporate into the DNA while inhibiting the guanosine nucleotide synthesis de novo pathway. It is cytostatic on lymphocytes as mycophenolic acid inhibits the critical dependency of the de novo pathway of purine synthesis, through which T- and B-lymphocytes proliferate. It is typically administered orally in the form of tablets, whether coated, delayed-release, or as a suspension, and as lyophilized or powder for injection. Similar to AZA, MPA's mechanism of action interferes with the de novo synthesis pathway of nucleotides, with a cytostatic effect on lymphocytes. Mycophenolic acid has a mean half-life of 8–16 hours and an MPAG metabolite half-life of 13–17 hours, but its route of elimination is not understood. It was introduced as a new drug in patients with lupus nephritis and renal problems who were unresponsive to conventional immunosuppressants [82]. MPA is available as a prodrug mycophenolate mofetil (MMF) and mycophenolate sodium (Myfortic) that increases MPA bioavailability and lessens gastrointestinal side effects, respectively [83]. MPA treatment has been reported to lessen the SLE complications combined with other immunosuppressive drugs, such as corticosteroids and antimalarials, when the disease was inadequately controlled with the previous non-MPA treatment regimens. Mycophenolate mofetil is most frequently used for induction or maintenance therapy of lupus nephritis and is effective in treating nonrenal symptoms as well. Typical symptoms of adverse effects include leukopenia, neutropenia, abdominal pain, diarrhea, nausea, vomiting, and dyspepsia. Mycophenolate has a potential teratogenic effect. Pregnancy case studies show that mycophenolate consumption during pregnancy causes major adverse effects including early, spontaneous, and elective terminations and abortions, fetal malformations and congenital defects, and premature and low-birth-weight newborns, [84]. As a result, female SLE patients have been prescribed AZA instead of mycophenolate when they become pregnant [85].

2.5 Cyclophosphamide

Cyclophosphamide (CP) is an inactive prodrug that requires enzymatic activation, which occurs by the hepatic cytochrome P-450 [86]. Cytochrome P-450 hydroxylates

the oxazaphosphorine ring of cyclophosphamide, thereby generating 4-hydroxy-cyclophosphamide, which coexists with its tautomer aldophosphamide. Upon decomposition, this aldophosphamide yields phosphoramide mustard, which acts as the alkylating effector, thereby exhibiting the cytotoxicity of CP. Interestingly, immunosuppression with cyclophosphamide has been identified as effective against life-threatening autoimmune disorders, such as SLE. SLE is characterized by B-cell hyperactivation and subsequent autoantibody production, often accompanied by T-cell abnormalities [87]. Under these conditions, cyclophosphamide has been beneficial as it effectively suppresses B-cell activity and antibody production [86]. Clinical studies in murine and human models showed that cyclophosphamide was more effective than prednisone in stabilizing renal function when given orally or intravenously. Standardization of medication revealed that long-term courses of cyclophosphamide alone or in combination with high doses of corticosteroids had a lower probability of doubling serum creatinine and renal function preservation [86]. A 6-month treatment regimen with cyclophosphamide significantly improved renal function and complement activity. Over the last years, IV cyclophosphamide is one of the standards of care for induction of remission therapy that is used in severe lupus nephritis due to its ability to slow the progression to end-stage renal failure and it has been shown to be also effective for the treatment of severe nonrenal symptoms, such as vasculitis and myocarditis. While cyclophosphamide is beneficial, it should be noted that its administration is associated with significant adverse effects, including nausea and vomiting [88]. Cyclophosphamide, like other cytotoxic medicines, has teratogenic side effects. Among the most acute toxicities of CP are cytopenias, infections, gonadal failure, and malignancies [86]. Some infections, including herpes zoster, are more common than others in these patients; hence regular vaccinations are recommended. While the overall standardized incidence ratio of cancer is higher in SLE patients, administration of CP has been shown to increase the incidence of cancers, particularly those of the urinary tract, bone marrow, and skin, prompting the use of combination therapy to prevent these side effects [89]. A recent randomized clinical trial in Chinese SLE patients comparing cyclophosphamide and tacrolimus has shown that tacrolimus has a marginally higher rate of complete response and faster recovery of kidney function [90]. In contrast to this, another trial showed that combination therapy of cyclophosphamide with rituximab followed by belimumab not only lowered the maturation of transitional to naive B cells during B-cell reconstitution but also improved the negative selection of autoreactive B cells, thereby proving beneficial over the conventional cyclophosphamide and belimumab combination [91]. When cyclophosphamide is contraindicated due to a previous severe reaction or malignancy, or there is a concern for drug toxicity, mycophenolate mofetil or rituximab or belimumab is recognized as an alternative immunosuppressive agent to cyclophosphamide for the treatment of lupus nephritis.

2.6 Voclosporin

The use of calcineurin inhibitors (CNIs) voclosporin is an effective therapy against lupus nephritis, a common and serious consequence of SLE. CNIs bind to and inhibit calcineurin, a calcium-dependent phosphatase, preventing T-cell activation, and T-cell-mediated immune response leading to attenuation in the inflammatory process in lupus nephritis [92]. Voclosporin has a modified functional side chain and was found to have a fourfold increase in potency by inducing structural changes in calcineurin. The modification increased the effectiveness of this drug and improved

the clearance of metabolites from the system. Thus, voclosporin was effective against lymphocyte proliferation, T-cell antigen presentation, and cytokine production [92]. According to the results of phase II clinical trial, females treated with voclosporin exhibited a 25% reduction in urine protein creatinine ratio after 8 weeks of treatment, as well as better complement activity after 24 weeks of treatment [93]. Interestingly, by the end of 24 and 48 weeks, the majority of patients had achieved remission, indicating that voclosporin was well tolerated in SLE patients. Another randomized double-blind placebo-controlled multicenter trial called AURA-LV, found that both low-dose and high-dose voclosporin administration promoted complete remission much more than the placebo group in a heterogeneous population [94–96]. Moreover, these patients had reduced anti-dsDNA antibody levels by 48 weeks, indicating the effectiveness of the medication. However, the study reported that patients receiving voclosporin experienced at least one adverse effect. Infection was the most common, under low-dose and high-dose administration, with a mortality of 5% [94]. Common adverse effects of the people who died in the low dose administration group include acute respiratory distress syndrome, infection, and thrombosis. Infection and pulmonary embolism were both common adverse outcomes in the high-dose administration deaths, showing that this medicine could have safety concerns [94]. Furthermore, the AURORA1 clinical trial in lupus nephritis patients found that adding low-dose voclosporin to a regimen of MMF given with low-dose corticosteroids significantly improved the therapeutic effects, with stable kidney function and no increase in the incidence of adverse effects [97].

2.7 Tacrolimus

Tacrolimus is a calcineurin inhibitor studied for its effects against SLE [98]. Tacrolimus has been recognized for its immunosuppressive effects and has found extensive use as a post-transplant drug. Mechanistically, tacrolimus binds to FK-binding proteins in the cytoplasm, forming a complex associated with the calcium-dependent calcineurin/calmodulin complexes to inhibit calcium-dependent signal transduction lymphocytes and resultant cytokine production [98]. The initial report on tacrolimus' efficacy against SLE came from a patient study in which cyclophosphamide and cyclosporine treatment was shown to be ineffective. Tacrolimus treatment reduced creatinine levels and eliminated digital vasculitis and gangrene in these patients [99]. Furthermore, tacrolimus had a significant impact on treatment-resistant cutaneous lupus erythematosus [100]. Another study in mice with spontaneous lupus nephritis found that tacrolimus reduced proteinuria slowed nephropathy progression and increased the lifespan of the lupus mice. Moreover, tacrolimus reduced the elevation in anti-ds DNA antibodies seen in SLE patients [101, 102]. A previous patient study showed that patients administered with tacrolimus for a year had a significant decrease in the SLEDAI (SLE Disease Activity Index) compared to nontreated patients [103]. Moreover, patients exhibited decreased anti-dsDNA antibodies and increased C3 concentration, indicating improved complement activity. While these patients developed minor adverse effects, such as tremors and headaches upon tacrolimus administration, the effects subsided gradually, indicating the medication's effectiveness and safety [103]. In addition to its efficacy in SLE patients without renal involvement, tacrolimus was effective in pediatric SLE patients with lupus nephritis who had persistent disease activity despite conventional immunosuppressive therapy [104]. Subsequently, multiple studies showed the effectiveness of tacrolimus in SLE patients through its improvements in renal function and targeted

immunosuppression [98], thereby proving it as an effective therapeutic agent that functions against SLE through multiple mechanisms. In a meta-analysis of several randomized controlled trials, case-control studies, and cohort studies, it was found that tacrolimus in combination with glucocorticoids resulted in higher total remission rates, lower proteinuria levels, and a lower SLE activity index than cyclophosphamide, indicating that tacrolimus is a safe and effective therapy against SLE [105]. Another trial indicated that tacrolimus is as effective as and non-inferior to mycophenolate mofetil in reaching a complete renal response rate, demonstrating its value as a lupus nephritis induction therapy [106]. Combination therapy has demonstrated encouraging results in the treatment of patients with refractory lupus nephritis, with the potential to improve disease control and prevent lupus nephritis flares. Both mycophenolate mofetil and tacrolimus combination have synergistic efficacy and favorable adverse event profile; therefore, they can be utilized to treat refractory lupus nephritis.

3. Therapy with biologics

During the past decade, a new class of therapeutics called biologics has been introduced, and their use led to successful treatment outcomes for lupus and several other inflammatory diseases. Biologics are proteins capable of binding to specific receptors present in immune cells and modulating the functions of immune cells. Overall, biologics are now being developed against several types of immune cells to modulate the functions of the immune system to treat the disease (**Figure 1**). Belimumab, a biologic that targets B cells, has been approved for the treatment of SLE. A number of biologics are now being studied in clinical trials (**Table 1**).

3.1 Anifrolumab

Anifrolumab, a type I interferon receptor antagonist, was recently approved in 2021 for the treatment of SLE in patients with moderate to severe symptoms [107].

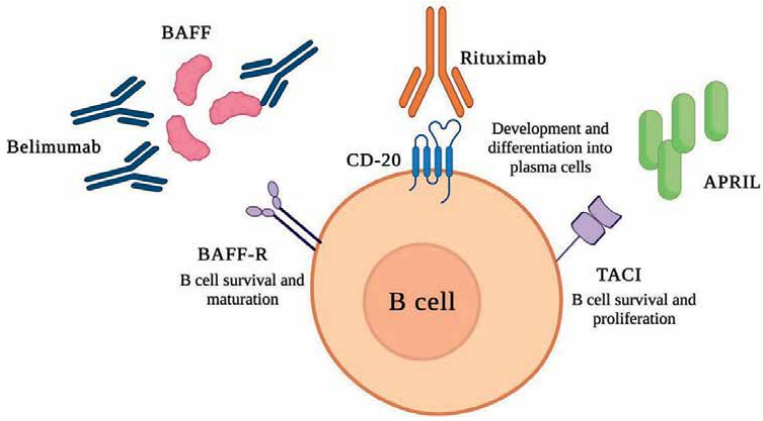

Figure 1.
Mechanism of action of belimumab and rituximab. Belimumab competitively inhibits BAFF binding to the BAFF receptor required for B-cell survival and maturation. Similarly, rituximab inhibits CD-20 on the surface of B cells, which inhibits B-cell maturation into plasma cells.

Drugs	Type	Target cell/ molecule	Mode of action	Clinical trial	Side effects	References
Obinutuzumab	Humanized anti-CD20 monoclonal antibody	CD20 on B-cell	Binding to CD20 on B-cell which causes complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity	Phase III	Neutropenia, Anemia, Pyrexia, Musculoskeletal disorders, Cough, Infusion reactions, Thrombocytopenia, Hepatitis B virus reactivation	
Daratumumab	Humanized anti-CD38 mAb	CD38 marker on plasmablasts	Binds to CD38 and causes apoptosis by triggering ADCC, complement-dependent cytotoxicity	Phase II	Infusion-related reactions (IRRs), face swelling, skin rashes	
Ustekinumab	Human monoclonal antibody against p40 subunit of IL-12 and IL-23	p40 subunit of IL-12 and IL-23	Prevent these molecules from binding to their receptors	Phase II discontinued during phase III	Dizziness, joint pain, headaches, sore throat	[21]
Obexelimab	Humanized Fc-engineered anti-CD19 mAb	CD19 on B-cell	Co-engages BCR and FcγRIIb on B-cell and inhibits B-cell activation	Phase II	Not known	
Lulizumab	Humanized PEGylated anti-CD28 dAb (Domain antibody)	CD28 on T-cell	Binds to CD28 receptor and inhibits T-cell proliferation and cytokine production	Phase II	Not known	
VIB7734	Anti-1LT7 Monoclonal antibody	Plasmacytoid dendritic cells	Deplete pDCs through ADCC	Phase II	Not known	
BIIB059	Humanized IgG1 monoclonal antibody	BDCA2 (blood dendritic cell antigen 2) receptor pf pDCs	Causes rapid BDCA2 internalization and impedes IFN production by plasmacytoid dendritic cells which leads to IFNGS (Type I interferon gene signature) expression in blood	Phase II	Risk of infection because of diminished pDC-mediated antiviral response	[21]

Drugs	Type	Target cell/ molecule	Mode of action	Clinical trial	Side effects	References
Telitacicept	Recombinant TACI-Fc (transmembrane activator and calcium modulator and cyclophilin ligand interactor) fusion protein	BLyS (B-lymphocyte stimulator) and APRIL (a proliferation-inducing ligand)	Binds and neutralizes the activity of BLyS and APRIL, thereby, inhibiting the development and survival of mature B cells and plasma cells	Phase II	Upper respiratory tract infection, reactions at the injection site	[21]

Table 1.
Biologics currently under clinical trial for the treatment of SLE.

Previous studies have indicated that type I IFN plays a key role in the pathophysiology of SLE and increased type I IFN signaling causes increased disease activity. Previous studies have demonstrated that type I interferon plays a key role in the pathophysiology of SLE and increased type I interferon signaling results in increased disease activity [108, 109]. The efficacy and safety data were obtained from the two TULIP phase III trials, and the MUSE phase II trial led to the approval of Anifrolumab [108, 110–113]. These trials were randomized, double-blinded, and placebo-controlled trials involving patients with moderate to severe SLE, who were under standard therapy with glucocorticoids, antimalarials, or immunosuppressants. In these trials, SLE patients treated with Anifrolumab experienced an overall reduction in disease activity in almost all organs, especially in skin and joints, and achieved a considerable reduction in the requirement of corticosteroids [107]. Further data suggest that Anifrolumab prevents organ damage occurring due to SLE or by chronic medications, including steroids, and thus, it improves the quality of life of SLE patients. The major adverse effects of Anifrolumab usage are mostly respiratory tract associated, including nasopharyngitis, bronchitis, and upper respiratory tract infections [107, 108, 110–112].

3.2 Rituximab

Rituximab (RTX) is a monoclonal antibody targeting CD20, a membrane receptor present on the surface of B-lineage cells, as a transmembrane protein excluding plasma cells and pro-B cells [114–116]. The interaction between CD20 and RTX results in the inaccessibility of CD20 for its ligand, leading to the inhibition of distinct cell survival pathways and B-cell maturation signals. Furthermore, the binding of rituximab with this membrane receptor results in the induction of both antibody and cell-mediated cytotoxicity, which causes the reduction of $CD20^+$ cells [116]. The FDA initially approved RTX for non-Hodgkin's lymphoma; it has also provided promising results in rheumatoid arthritis (RA) treatment. Based on recent studies, RTX may have a beneficial role in inflammatory diseases [117]. In 2002, RTX was used to treat SLE; RTX was used in combination with steroids and cyclophosphamide; five out of six patients developed significant improvement in response to this treatment [118, 119]. RTX showed significant beneficial results in phase I and phase II clinical trials; another retrospective clinical trial performed on 45 patients showed the beneficial effects of RTX [120]. Phase II and phase III trials, known as the EXPLORER trial, were conducted based on the positive outcomes of RTX treatment in SLE. The main aim of this trial was an extensive analysis of RTX efficacy in nonrenal SLE. This trial comprised 257 patients who were kept on a stable dose of one immune-suppressive drug were included in this study; these participants were treated by following a standard care of treatment, along with either two intravenous RTX 1 g doses (one at 14 days following the start of the trial and the other at 6 months) or placebo. The use of methotrexate, azathioprine, mycophenolate mofetil (MMF), and corticosteroids was allowed for continuation under the supervision of treating medical specialists. The primary endpoint of this study was to achieve and maintain a robust clinical response or a partial clinical response by the 52nd week. The secondary endpoint was to assess the clinical response of patients at 52 weeks, along with the improvement in quality of life. The steroid-sparing benefit of RTX was also evaluated as a secondary endpoint. No difference between the primary and secondary endpoints was observed in the RTX and placebo groups for this EXPLORER trial. Another trial, known as LUNAR, was conducted in SLE patients to investigate the efficacy of RTX

in lupus nephritis [121]. It was a double-blind RCT with 144 participants, and the amount of RTX dosage and other standards of care treatments were similar to the EXPLORER trial. There was no significant difference between the RTX and placebo cohorts' primary and secondary endpoints [121]. Although the endpoints of phase II and phase III RCTs for rituximab failed, this does not necessarily mean that the drug failed; trial design can be considered as a possible potential reason for this failure. RTX has some adverse effects. RTX use is contraindicated in advanced heart failure (New York Heart Association Class IV) [122]. Since RTX is an immunosuppressant, infection is a significant concern with rituximab treatment. Several studies have shown that repeated use of RTX can be associated with decreased immunoglobulin levels. Patients who already have low immunoglobulins or are already taking other immunosuppressant medication have a higher rate of infection while taking RTX treatment [123].

3.3 Belimumab

Belimumab (BEL) is a monoclonal antibody that targets BAFF [124] and is referred to as a B lymphocyte stimulator (BLyS); these factors are secreted by myeloid-lineage cells. The binding of BAFF with BAFF-R (receptor present on B naïve cells) leads to the activation of specific signaling, promoting survival and differentiation of the naïve B cells [125]. BEL binds with these soluble stimulatory factors, resulting in the inhibition of BLyS binding with BAFFR [124, 126]. BEL was first approved for adult SLE in 2011, with remarkable success in adult SLE treatment. A study performed on mice models has demonstrated the importance of BAFF in SLE progression, where deletion of the Baff gene prevented SLE progression in diseased mice [127]. Neutralizing BAFF with specific immunogenic approaches in mice has shown a significant reduction in disease progression [128, 129]. Patients suffering from SLE have shown a higher level of BAFF than healthy controls, and the level of BAFF was found to be increased in the correlation with SLE progression [130–132]. Efficacy of BEL against SLE was initially studied in a large double-blind phase III RCTs [133, 134]. In this study, 10 mg/kg intravenous BEL was given in addition to the background standard of care therapy with a 2-week interval between the first three doses and then every 4 weeks. SLE patients who had active CNS involvement or lupus nephritis were excluded. Participants were kept on stable doses of corticosteroids, antimalarials, nonsteroidal anti-inflammatory drugs, and immunosuppressive drugs for 30 days before this trial. The primary endpoint was the SLE responder index-4 at week 52. This accounted for ≥4-point depletion in the SLE disease activity index (SELENA-SLEDAI) score. The significant difference between the patient and placebo arm of the trial study has given promising results for BEL use against SLE. Consistently, BEL effectively improved SLE in all the trials compared to placebo. BEL has also shown steroid-sparing effects in these patients [135, 136]. Moreover, in the ongoing international observational clinical studies, BEL is being used as a part of the treatment routine in more than 700 patients and has shown remarkable beneficial effects [137–139]. Despite being a remarkable drug against SLE, and being an immunosuppressor drug, BEL also has some contraindications along with minor side effects. Major infections have been observed in the patients treated with belimumab. Appropriate precautions and medical advice should be taken by the patient suffering from chronic infection before the BEL treatment [124]. In patients with refractory LN, studies showed that adding belimumab to a therapy regimen that included rituximab/CYC was safe and effective [140]. Moreover, BEL, despite being a safe drug,

not all the patients treated with BEL show significant improvement in their disease. This suggests the involvement of other vital pathways playing a role in SLE development which challenges the generalized use of BEL against SLE.

4. Conclusion and future directions

SLE is a complex and devastating disease. Without a possible cure in sight, patients with SLE rely on treatment based on symptoms to improve their quality of life. In recent years, there have been an increasing number of clinical trials with novel biologics that give hope to further improvements in the therapy of SLE. However, a knowledge gap exists in the current understanding of the molecular basis of SLE. Understanding the basis of susceptibility to SLE could open avenues to treat the disease at an early stage before it progresses to severe systemic disease. Primary research is needed to uncover the cause of the disease and, specifically, the reason for the development of autoantibodies, immune system dysfunction, and chronic inflammation. The determinants of disease severity are unknown, challenging current treatment regimens. The existing treatments for SLE usually include immunosuppression, which predisposes patients to infection, the primary cause of premature mortality in SLE patients. From the therapy point of view, it is essential to identify the underlying genetic and epigenetic profiles, immune mechanisms, and the severity of the disease to deliver personalized therapy.

Conflict of interest

The authors declare no conflict of interest.

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Chapter 3

Lupus Nephritis: Clinical Picture, Histopathological Diagnosis, and Management

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Abstract

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder that can affect almost every organ of the body and presents with a great variety of clinical features. SLE effect on kidneys, mostly referred to as lupus nephritis, is of special interest for the rheumatologist and nephrologist for three reasons. First, lupus nephritis is one of the commonest types of organ involvement in this disorder, affecting as up to 45% of all patients with SLE. Second, it presents with a great variety of clinical and histopathological findings, and thus, therapy must be tailored accordingly. Third, it greatly affects the morbidity and mortality of SLE patients. Taking these facts into account, this chapter is centered on lupus nephritis from the perspective of the clinical nephrologist and renal pathologist. This chapter elaborates the diversity of clinical features of lupus nephritis, in relation to the different histopathological forms of the disease and the therapeutic options that are available to date, as well as the pathogenesis, natural history, and prognosis of patients with lupus nephritis.

Keywords: lupus nephritis, histopathology, prognosis, management, end-stage kidney disease (ESKD)

1. Introduction

Systemic lupus erythematosus (SLE) is a multisystemic autoimmune disease with high heterogeneity. The hallmark of SLE pathogenesis is the production of autoantibodies [1], which results from a combination of genetic, epigenetic, environmental, hormonal, and immunoregulatory factors [2]. The heterogeneity is expressed with different clinical phenotypes that range from which organs are inflicted to the way that disease is caused at a specific organ and can be attributed to different autoantibody profiles, genetic variants, and interferon levels [3]. For example, there are two different phenotypes in patients with neuropsychiatric lupus [4], while there is a spectrum of different phenotypes concerning joint involvement in SLE [5]. This wide heterogeneity has even prompted researchers to question if SLE is a single disease [6] and highlights the difficulty of defining SLE. As a result, the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) have developed criteria

to classify patients' disease as SLE. According to the most recent edition of these criteria [7], all patients considered to be classified as SLE must have a positive antinuclear antibody test and must accumulate certain clinical and immunological criteria.

Kidney involvement in SLE is a common and potentially life-threatening form of the disease. There are diverse ways with which SLE can cause kidney disease, such as lupus podocytopathy [8], tubulointerstitial disease [9], and syndromes like thrombotic thrombocytopenic purpura [10], but the usual form of kidney involvement is lupus nephritis (LN). LN is a form of glomerulonephritis in patients with SLE [8], which is characterized by the presence of stains for immunoglobulin G (IgG), immunoglobulin M (IgM), C3, and C1q in the immunofluorescence (IF) [11]. Patients with LN have been shown to have higher rates of morbidity and mortality compared with patients without renal involvement. There are different classes of LN that present with different clinical signs and have different prognosis [8].

2. Epidemiology of lupus nephritis

SLE is a disease with a prevalence ranging between 30 and 50 cases per 100,000 people worldwide [12]. In the USA, the incidence of SLE is estimated between 5.5 and 7.4 cases per 100,000 persons-years [13]. In Europe, where there are discrepancies between different national SLE registries, the estimated incidence of SLE varies between 1.5 and 7.4 per 100,000 persons-years [14]. In South America, the incidence varies between 1 and 4.2 cases per 100,000 persons-years [14], while in Asia, incidence ranges between 2.8 and 8.6 cases per 100,000 persons-years; in Australasia, there are at least 11 cases per 100,000 persons-years [14]. These data showcase that the prevalence and incidence of lupus in a population is related to the ethnicity of the population. In the USA, it was shown [13] that SLE is commoner in African American, then in Hispanics, and is less common in Caucasian. It is widely known that 90% of patients with SLE are women [12]. In this regard, gender and ethnicity impact the incidence and prevalence of SLE.

The frequency of LN varies between different regions of the world and different ethnicities. Overall, 30–60% of patients with lupus and 70% of children with SLE develop LN [15]. It has been shown that LN is more frequent in the Black population with SLE than in Asians and Hispanic populations and less common in Caucasians [16]. The difference in frequency can be attributed to "high-risk" genotypes. For instance, a significant association between the known "high-risk" APOL1 alleles and LN has been shown [17]. These alleles can be found in Black patients, explaining the higher prevalence of LN in these patients. LN has a significantly higher frequency in male patients with SLE when compared to females [18–20]. Furthermore, LN is more common in patients with childhood onset lupus when compared with adult-onset lupus [21].

3. Pathogenesis of lupus nephritis

The pathogenesis of LN is complex with distinct factors (genetic, hormonal, and environmental) influencing the natural course of the disease [22]. The bottom line of LN pathogenesis is the production of autoantibodies against autoantigens, with double-stranded DNA being the commonest target [23]. There are two ways that anti-ds DNA antibodies exert their nephritogenic effect. First, immune complexes are formed in the circulation that are deposited to the glomeruli. Second, anti-ds DNA antibodies

are connected to the glomeruli *in situ* either by binding to exposed chromatin fragments connected to glomerular membranes and mesangial matrices or by binding to non-DNA structures connected to the glomerulus that cross-react with anti-ds DNA antibodies [22, 23]. All these models are required for the fragments of chromatin to be exposed for anti-ds DNA antibodies to be produced. Seredkina et al. [24] showed that this chromatin exposure is achieved in mice because of renal DNAse1 deficiency, leading to reduced clearance of apoptotic material. The surplus apoptotic material led to a surge of anti-ds DNA levels and the formation of mesangial immune deposits [25]. Reduced levels of renal DNAse1 have been observed in humans with LN as well [25]. It must be noted that not all anti-ds DNA antibodies are nephritogenic [26]; only a subset is able to get deposited in the kidney. It has been shown that autoantibodies against annexin-a2 [27] and autoantibodies against moesin [28], antigens found in the glomeruli, cause proliferative LN. At the same time, patients with membranous LN present with immune complexes consisted by exostosin-1/exostosin-2 antigens and autoantibodies [29] and immune complexes with neural cell adhesion molecule 1 [30]. It can be assumed that this great heterogeneity in SLE autoantibodies is the reason behind the different classes of LN.

The surplus apoptotic material described before activates dendritic cells, monocytes, and macrophages [22]. These cells, through the production of cytokines and the presentation of autoantigens, activate effector B cells by prolonging their survival and maturation process. This way, the number of autoreactive B cells, memory cells, plasma cells, and produced autoantibodies is increased [22]. Recently, a new function of B cells has been discovered. Besides their function as antibody-producing cells, B cells seem to aggregate in inflamed organs creating complex structures that are called tertiary lymphoid tissue [31]. This tissue form ranges from small clusters of lymphocytes to sophisticated structures reminiscent of lymph nodes. This tissue is observed on kidneys in a variety of different diseases from chronic pyelonephritis to autoimmune disease. Their role is to produce *in situ* autoantibodies and proinflammatory cytokines, activate T cells, and cause lymph angiogenesis [32]. Shen et al. [33] showed that intrarenal B cell infiltrates were found in 60% of patients with LN and were associated with LN class IV, greater activity and chronicity indices, and worse glomerular filtration rate (GFR). It can be deduced that B cell infiltrates in patients with LN are related to worse outcome.

Besides the proliferation of autoantibody-producing B cells, the surplus apoptotic material triggers innate immunity [8]. The surplus apoptotic material leads to the formation of neutrophil extracellular traps (NETosis) by neutrophils [34]. NETosis is a sequence of cellular events leading to the programmed death of neutrophils and the production of these "traps" (NETs). NETs are web-like DNA structures decorated with histones and cytotoxic proteins, and their role is to trap and destroy pathogens [35]. In sterile conditions, NETs, through their functions, can exacerbate inflammation. First, NETs are a potential source of autoantigens leading to the production of autoantibodies and the formation of immune complexes. Second, NETs serve as a platform for complement activation that leads to inflammation exacerbation and cellular damage. Third, NETs themselves contribute to kidney tissue damage by acting directly on kidney cells, creating microthrombi and releasing cytokines [36].

A critical step in the pathogenesis of LN is the activation of type I interferon system. It has been shown that NETs activate monocytes to produce cytokines such as interferon alpha [37]. However, most of the cytokines are produced by the plasmacytoid dendritic cells [38]. In lupus patients, these cells migrate to tissues (like renal

tissue) [38]. Then, immune complexes containing nucleic acids are internalized, reach the endosome, and stimulate the production of interferon alpha [39]. Under normal circumstances, type I interferons connect to type I interferon receptors that activate other pattern recognition receptors (like toll-like receptors 7 and 9). This cascade of events leads to the expression and stimulation of certain genes and their corresponding enzymes [38]. Some of the enzymes induced lead to the inhibition of viral reproduction [40] highlighting the role of the interferon system in antiviral immunity. At the same time, type I interferon enhances the cytotoxic abilities of natural killer (NK) cells and stimulates the maturation of dendritic cells to antigen-presenting cells [38]. In lupus patients, the overexpression of type I interferon leads to the overexpression of toll-like receptor 7. It has been shown in mice that this overexpression is related to clinically severe SLE [41]. Likewise, it has been shown that patients with nephritis present with an interferon signature and greater levels of interferon I [38].

Complement activation also plays a key role in LN pathogenesis. As already revealed, the first step in LN pathogenesis is the existence of surplus apoptotic material. Under normal circumstances, complement promotes apoptotic debris removal [42]. In patients with SLE, this complement's function is performed in a reduced rate. It has been found that many patients who develop LN present with anti-C1q antibodies [42]. These antibodies further reduce complement's capability of apoptotic debris removal and seem to induce a loop of activation of the classical pathway of complement. Then, the autoantibody mediated renal damage in LN seems to activate the complement via the classical and alternate pathway [43]. Moreover, complement factors like C3a and C5a attract neutrophils and potentiate their response (**Table 1**) [44].

4. Clinical phenotypes of lupus nephritis

The clinical phenotypes of LN are characterized by great heterogeneity, ranging from asymptomatic microscopic hematuria to nephrotic syndrome, to acute nephritic syndrome and rapidly progressive glomerulonephritis [18]. Specifically, Moroni et al. [45] showed that 49% of patients with LN present with isolated urinary

Mechanism	Way of activation	Effect
Surplus apoptotic material	Reduced renal DNAse1	Production of autoantibodies
Autoantibodies	Surplus apoptotic material	Activation of macrophages, dendritic cells
B cells	Cytokines by macrophages	Production of autoantibodies Aggregation for production of tertiary lymphoid tissue
NETs	Autoantibodies	Production of autoantigens Complement activation Tissue damage
Type I interferon	Plasmacytoid dendritic cells	Overexpression of toll-like receptor 7
Complement	Surplus apoptotic material Reduced ability of complement to remove apoptotic material	Tissue damage

Table 1.
Mechanisms related to pathogenesis of lupus nephritis.

abnormalities, 36% with nephrotic syndrome, 13% with acute nephritic syndrome, and 3% with rapidly progressive renal failure.

Despite the therapies that have been developed, a subset of patients reaches end-stage kidney disease (ESKD). The incidence of ESKD is estimated to be 2.3 patients per 1000 patient-years [46]. There are risk factors that help us identify patients at an elevated risk of developing end-stage renal disease. Some risk factors are demographic, like male sex, young age, and African or Hispanic ethnicity; some are clinical, like anemia, elevated serum creatinine, and hypertension on the biopsy time [47]; and some are histopathological, like proliferative nephritis (class III or IV) and high chronicity or activity indices [45]. It must be noted that the clinical phenotype cannot predict the class of LN. For example, in a series of 21 patients with SLE and isolated urinary abnormalities, the biopsies of 13 patients showed LN class III, IV, or V [48]. As a result, the EULAR proposed all patients with SLE and suspicion of renal involvement (glomerular hematuria and/or cellular casts, proteinuria >500 mg, or unexplained worsening of renal function) to be candidates for kidney biopsy [47].

5. Histopathology of renal involvement in patients with SLE

Lupus nephritis is an immune complex disorder of the kidney that may present with many faces, demonstrating a large diversity of clinical and pathological features among patients. Clinical features can range from asymptomatic urinary findings of microhematuria and mild proteinuria to full-blown nephrotic syndrome and/or rapidly progressive glomerulonephritis. Periods of remission and exacerbation are typically found during the course of the disease.

The pathological features can also be varied, including glomerular lesions, but also tubulointerstitial and vascular lesions. The major pathological findings are described in the LN Classification of 2003 by a consensus meeting of renal pathologists, nephrologists, and rheumatologists of the American Society of Nephrologists (ISN) and Renal Pathology Society (RPS), while previous classification schemes had been proposed by pathologists and nephrologists under the auspices of the World Health Organization.

The immune complex deposits can be found in mesangium and/or glomerular basement membranes, while sometimes deposits are recognized in tubular basement membranes and vessels walls. Therefore, a large diversity of immune-complex deposits can be found in LN, such as mesangial, subendothelial, and subepithelial, many times concurrently, while glomerular lesions can also be extremely varied, including mesangial, endocapillary, and/or glomerular basement membrane alterations. Glomerular pathological patterns can range from mesangial expansion and hypercellularity to endocapillary hypercellularity, membranoproliferative or membranous pattern, while in many instances, these patterns can coexist or overlap. Constant feature in all the classes of LN is the "full house" pattern in immunofluorescence examination, for example, expression of all immunoglobulins (IgG, IgA, and IgM) and complement components (C3 and C1q), as well as kappa and lambda light chains in the glomerular compartments. Additional findings revealed by electron microscopy (EM) examination include the common presence of "tubuloreticular" inclusions in endothelial cells and electron dense deposits within tubular basement membranes, while, sometimes, electron dense deposits can be found within small vessel walls. Uncommonly, organized mesangial deposits with tubulofibrillar substructure resembling seen in cryoglobulinemia or "fingerprint" laminated structures can also be encountered.

According to the distribution of glomerular tuft deposits that determines the type of proliferative response, the predominant resulting glomerular pattern, the extend of severity, any coexistence of glomerular patterns, and the presence of chronic lesions, LN is categorized in six classes according to the current classification (2003), while a few modifications have been proposed in 2016 and are discussed in detail later [49–51]. Electron microscopy (EM) examination is not required for defining the class of LN, since in many countries there is no EM facility. Data from light microscopy (LM) and immunofluorescence (IF) examination are usually enough for nephritis typing. On the other hand, EM can provide additional information, especially in some cases; thus, a small piece of tissue must be kept in glutaraldehyde for examination.

Class I is characterized by mesangial immune deposits in IF, but no morphological changes in light microscopy, according to the classification of ISN/RPS 2004. Urinary abnormalities are minimal and include microscopic hematuria with mild proteinuria, while renal function is normal. This is the mildest glomerular lesion in LN and is relatively rare, since these patients generally have no essential clinical renal abnormalities and are not referred to nephrologists for biopsy.

Class II is defined by purely mesangial hypercellularity of any degree, or mesangial matrix expansion by LM, with mesangial immune deposits. No subendothelial deposits visible by light microscopy are allowed for this class. Only few subendothelial or subepithelial deposits visible by IF or EM are allowed. Urinary abnormalities are mild and include microscopic hematuria with mild proteinuria, while renal function is usually normal. If nephrotic syndrome is observed, in an otherwise typical case of class II nephritis, with no subepithelial deposits, the possibility of lupus podocytopathy should be examined.

Class III includes active or inactive focal and segmental endocapillary and/or extracapillary glomerulonephritis involving <50% of all glomeruli, typically with focal subendothelial immune deposits with or without mesangial alterations. Microscopic or macroscopic hematuria and severe proteinuria are usually seen. Lupus serologies are usually active.

Class IV includes active or inactive diffuse segmental and/or global endocapillary and/or extracapillary glomerulonephritis involving ≥50% of all glomeruli, typically with diffuse subendothelial immune deposits with or without mesangial alterations. These patients have the most severe and active clinical renal presentation. Proteinuria can reach nephrotic level, and many patients (up to 50%) can present with nephrotic syndrome. Urine sediment is active, while red blood cell (RBC) casts are common. Renal insufficiency can be demonstrated by glomerular filtration rate (GFR), although serum creatinine can be normal, especially in young women with little muscle mass. Hypertension can be observed, while lupus serologies are active.

Class V includes membranous LN with global or segmental subepithelial immune deposits by LM and IF or EM, with or without mesangial alterations. Severe proteinuria or nephrotic syndrome is usually seen in many cases accompanied by microscopic hematuria. Renal insufficiency is uncommon.

Class IV includes advanced sclerosing LN. Urinary abnormalities consisted of proteinuria of varying degree with inactive sediment, while renal function is impaired. Hypertension is common, while lupus serologies may be inactive (i.e., "burnt-out" lupus).

There are also mixed classes in LN that include classes III and V and classes IV and V. In addition, an activity and chronicity index has been proposed [52] to determine the severity of disease, providing prognostic as well as therapeutic indications for patients' management.

Commonest classes in biopsies samples, according to various studies are classes III, IV, and V [53, 54]. Among the first five classes, classes III and IV have the worst prognosis. Classes III and IV are characterized by high activity. "Wire" loops (thickened eosinophilic glomerular membranes occupied by deposits), eosinophilic "hyaline" thrombi, and numerous inflammatory cells into capillary lumens including neutrophils, nuclear "debris," membranoproliferative pattern, glomerular crescents, and/or necrosis can be seen (see **Figures 1**–**4**). Numerous electron dense deposits in immunofluorescence and EM examination are usually seen in **Figures 5** and **6**.

Membranous LN is usually manifested with high proteinuria and nephrotic syndrome (up to 70%), while hematuria is found in up to 50% and renal insufficiency is uncommon (see **Figures 7** and **8**). On the contrary, high proteinuria with renal insufficiency and active urine sediment is common in mixed classes III and V or IV and V, so close pathological correlation with clinical data is required in every case.

In repeat biopsies, a "transformation" phenomenon has been described, from one class to another, usually after treatment, or spontaneously. Class III to class IV is a common transformation in repeat biopsies, but many authors prefer to interpret it as a transition along a disease continuum, rather than a true transformation. Mesangial proliferation is often seen after the treatment of class III or class IV LN, although ultrastructurally residual irregularities of the glomerular basement membrane consisted of resorbed and organized subendothelial deposits can be seen. Virtually, all directions of transformation have been described.

Some investigators have proposed that class IV-S is pathogenetically distinct from other LN. Schwartz et al. [55] described a category of "severe segmental

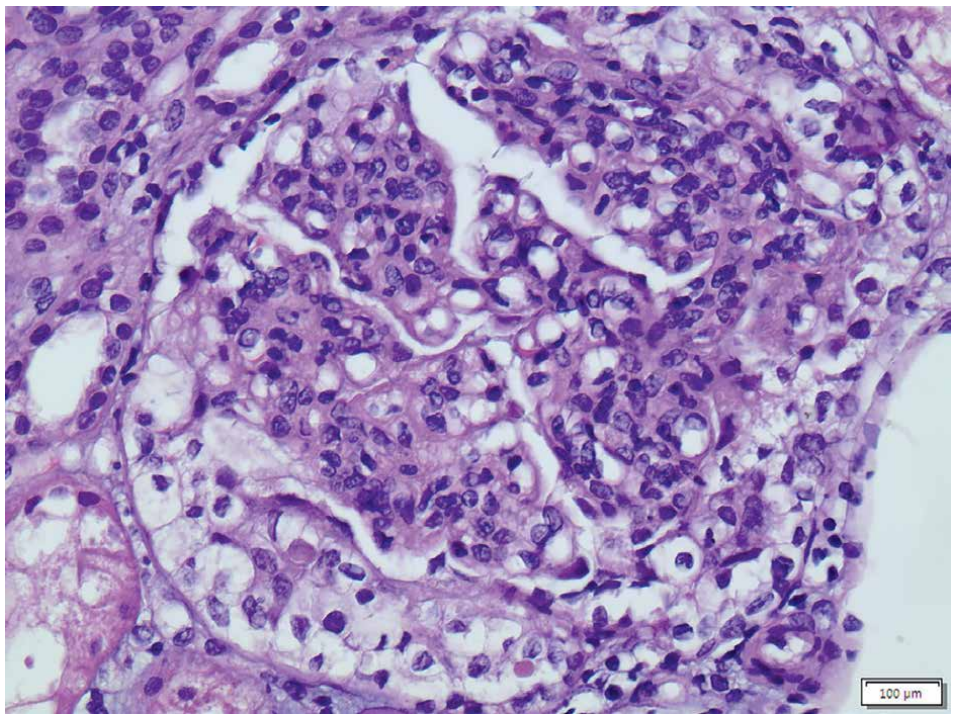

Figure 1.
Severe endocapillary cellularity/proliferation in association with crescent formation in the left corner [H&E X400].

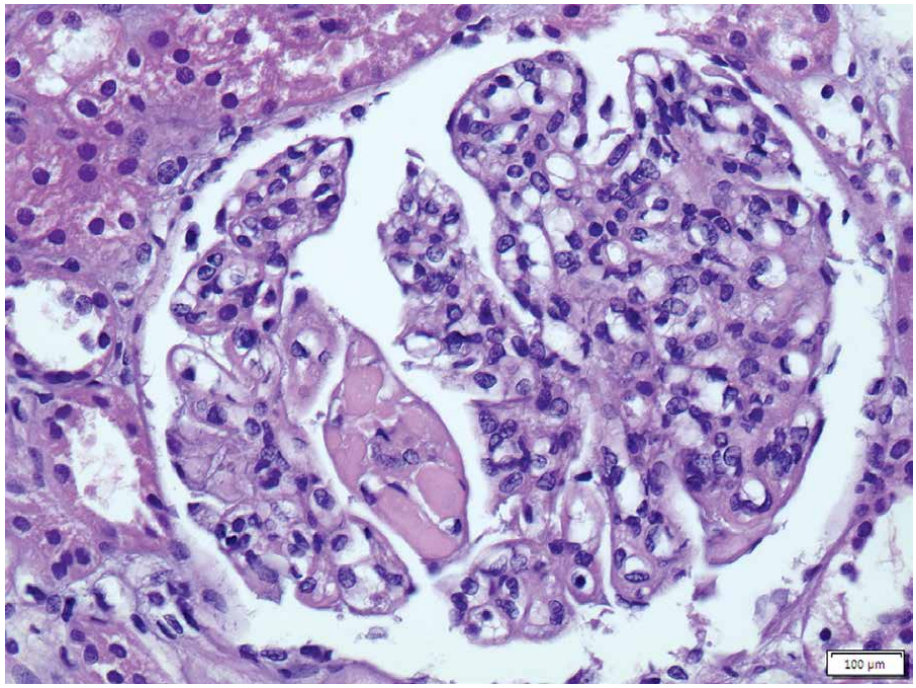

Figure 2.
Mesangial and endocapillary cellularity/proliferation in association with "hyaline" thrombi into glomerular lumens [H&E X400].

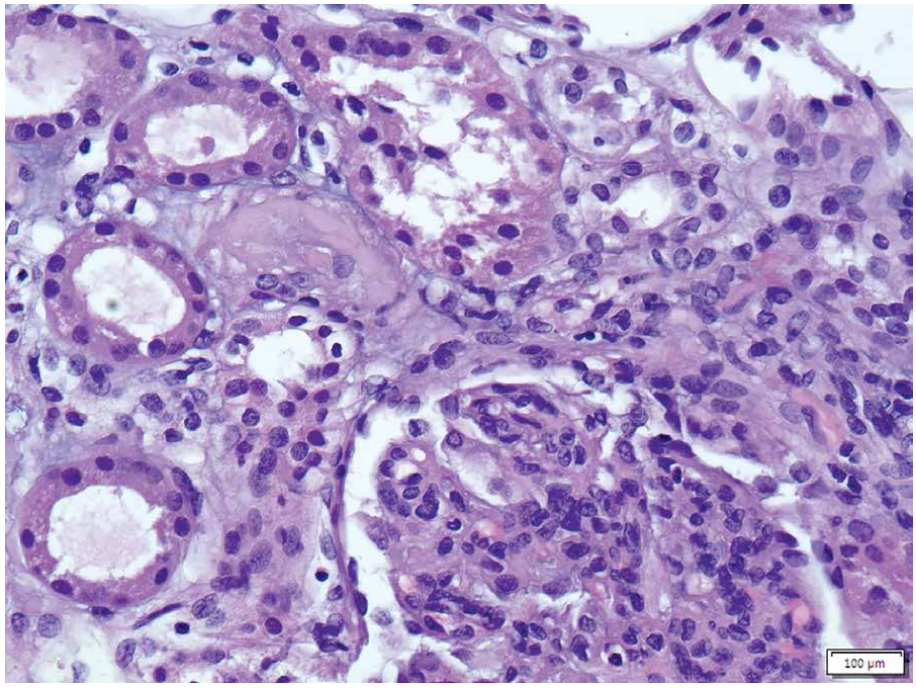

Figure 3.
Immune complex deposits in an arteriole, the so-called lupus "vasculopathy" [H&E X400].

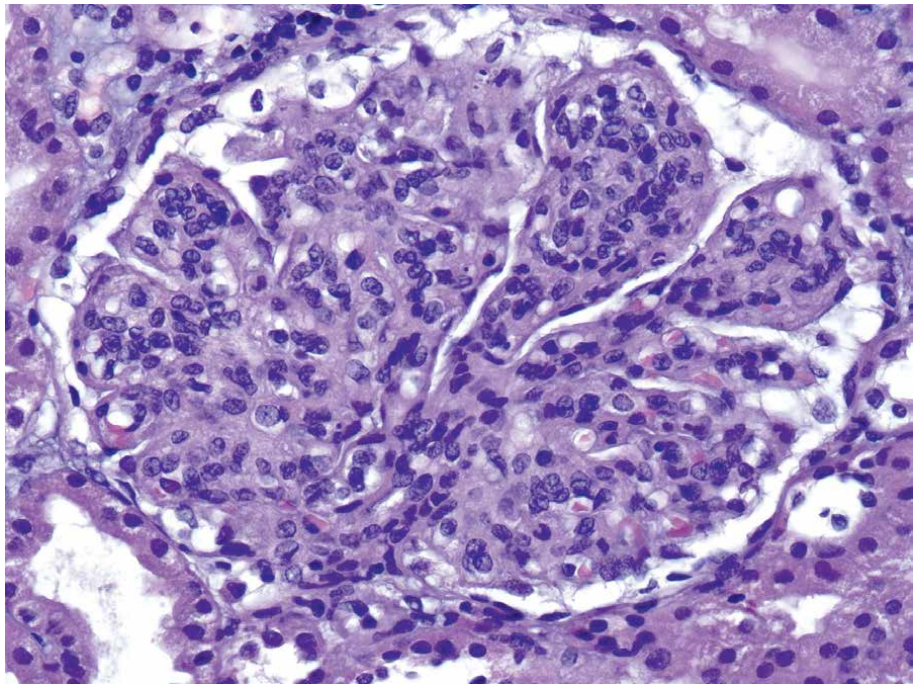

Figure 4.
Membranoproliferative pattern in LN [H&E X400].

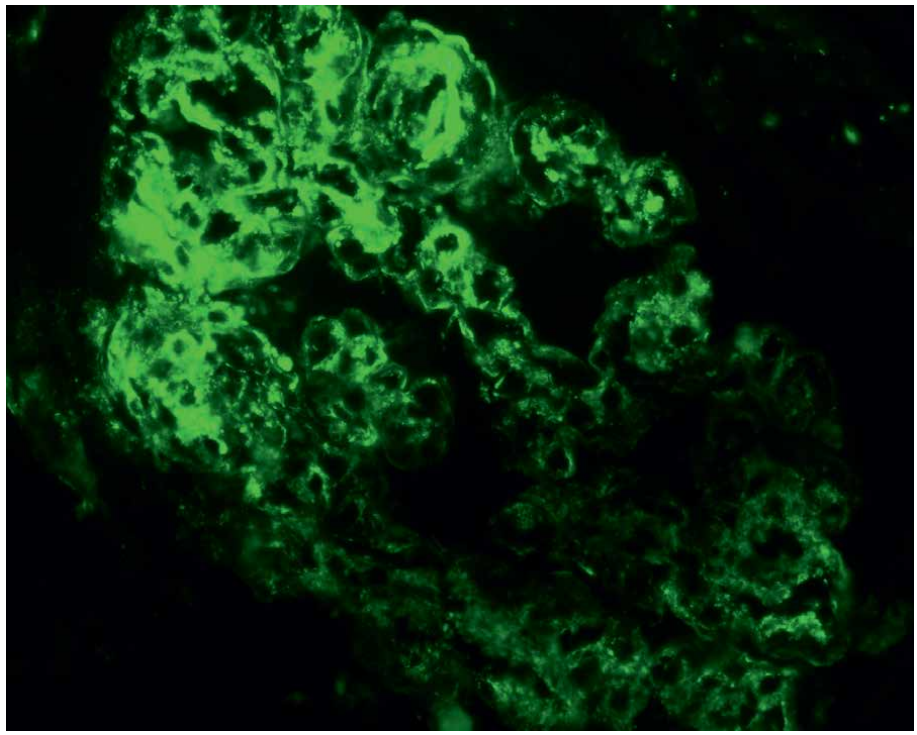

Figure 5.
Mesangial and large subendothelial deposits in immunofluorescence examination, in a case of class IV LN [C1q X400].

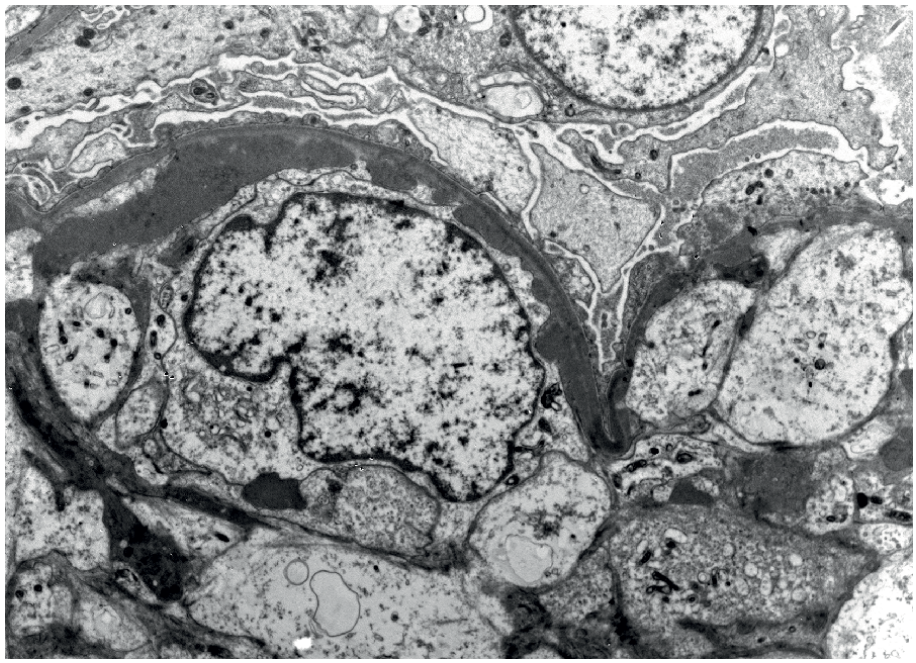

Figure 6.
Large subendothelial deposits in EM examination, in a case of class IV LN [uranyl acetate X 4400].

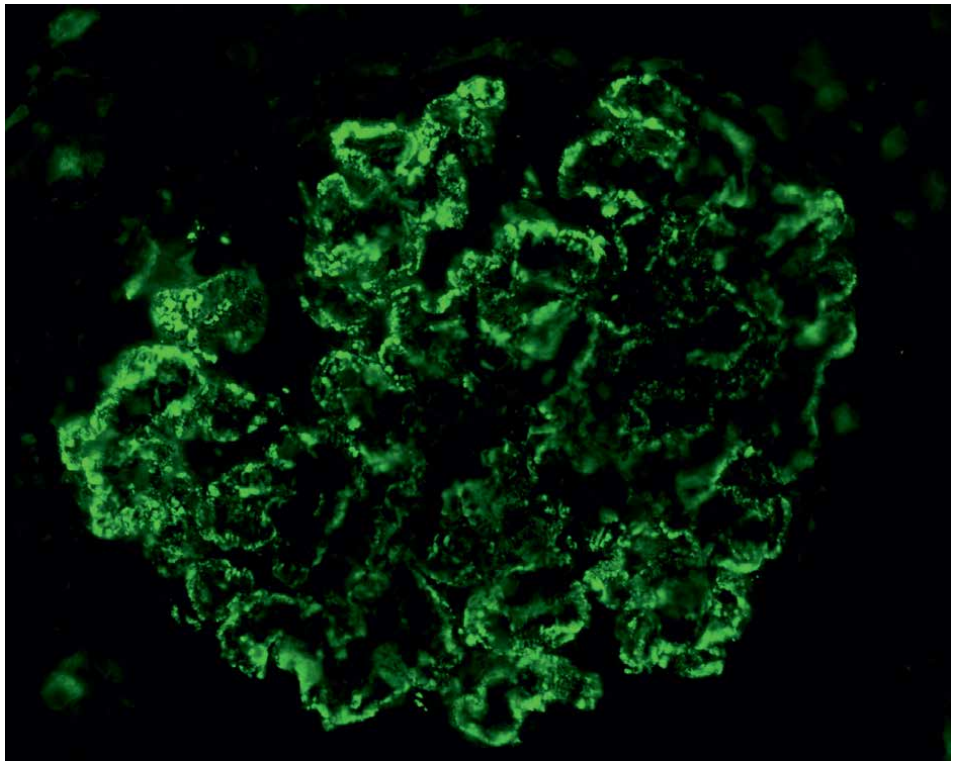

Figure 7.
Subepithelial deposits along glomerular basement membranes in a class V LN [immunofluorescence, IgGX400].

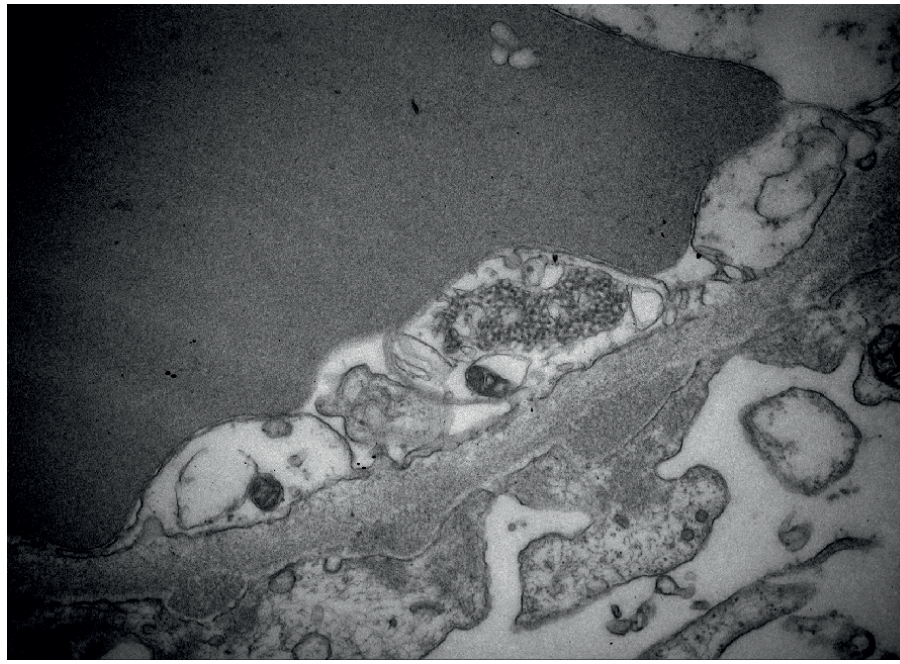

Figure 8.
Subepithelial deposits along glomerular basement membrane in association with a tubuloreticular inclusion in the cytoplasm of an endothelial cell, class V LN [uranyl acetate X 18000].

glomerulonephritis," in which the glomerular inflammation was predominantly segmental. This category is now designated as IV-S in the ISN/RPS classification. This category had an outcome measured in short-term renal survival that was intermediate between the classic focal and diffuse proliferative groups. The category IV-S was introduced because of evidence from the Chicago group that this subgroup has worse long-term outcome than IV-G, especially if associated with segmental necrotizing lesions and not endocapillary proliferation, possibly implicating pauci-immune necrotizing vasculitis mechanisms [56, 57]. In contrast, no difference in outcome was observed between these classes by the Boston group [58]. Typically, the subendothelial and mesangial deposits are larger and more abundant in class IV-G, as compared with classes III and IV-S, usually staining more intensely in immunofluorescence.

Clinical signs, such as proteinuria and hematuria, or creatinine level, as a solely marker are not enough to determine therapeutic options in LN, since it is well known that the discrepancy between the clinical and the pathological features in lupus patients, who are usually young, may compensate renal function. Furthermore, nephritis can be "silent" in lupus patients; that is an old observation. Thus, renal biopsy is necessary for disease control. Indications of biopsy include the confirmation of the disease, the confirmation of the kidney involvement in a patient with SLE, the determination of the type of involvement, the determination of disease severity, the determination of therapy, and prognostic implications. In addition, the extent of chronicity is evaluated in biopsy to determine if proteinuria or creatinine rising is due to activity or chronicity. If the latter predominates with no associated activity, unnecessary immunosuppression is avoided (see **Figure 9**).

According to a consent report by Bajema et al. [51] (after a meeting of 18 members of an International Nephropathology working group in Leiden, The Netherlands, in

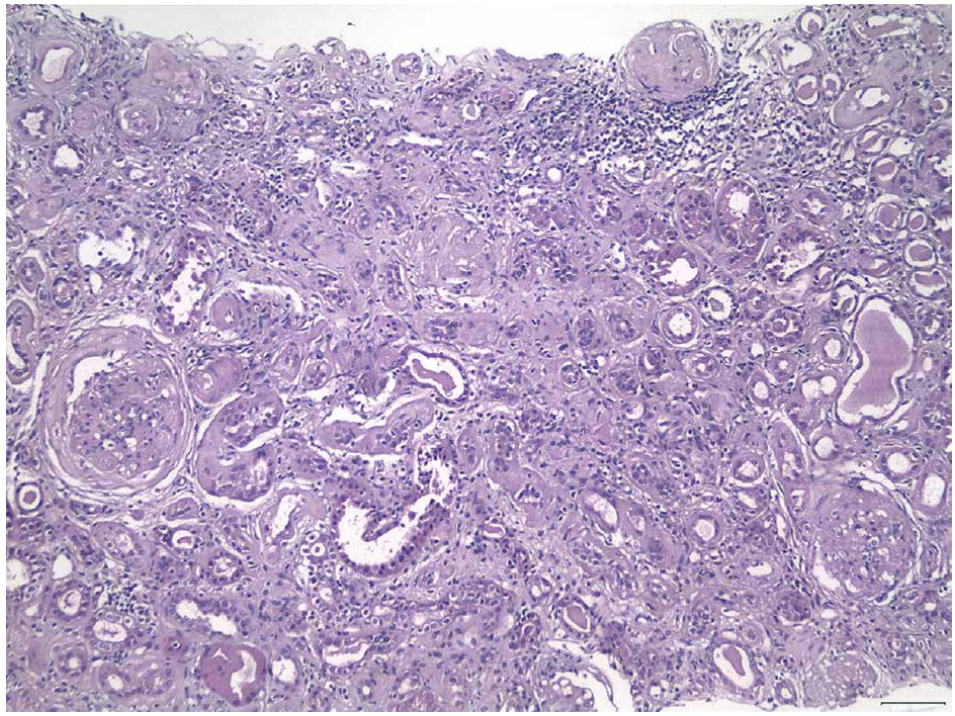

Figure 9.
Severe glomerulosclerosis, interstitial fibrosis, and tubular atrophy in a class VI LN [H&E X 100].

2016), the terms of segmental and global categories in class IV LN are eliminated. In addition, division in active/chronic categories for classes III and IV is replaced by an activity and chronicity score that should be provided in every pathology report. Fibrinoid necrosis is added in activity index, as an independent marker (activity index 0–24: endocapillary hypercellularity 0–3, neutrophils/karyorrhexis 0–3, hyaline deposits 0–3, fibrinoid necrosis 0–3 [x2], Cellular/fibrocellular crescents 0–3 [x2], and interstitial inflammation 0–3; chronicity index 0–12: total glomerulosclerosis 0–3, fibrous crescents 0–3, tubular atrophy 0–3, and interstitial fibrosis 0–3]. Other proposals of the same working group include an increase in the cutoff of mesangial hypercellularity from three to four mesangial cells (according to the definitions of Oxford Classification for IgA nephropathy), the replace of term endocapillary "proliferation" by the term endocapillary "hypercellularity," new definitions for crescents, etc.

Vascular lesions can also be encountered in LN, such as uncomplicated vascular immune deposits, noninflammatory necrotizing vasculopathy (lupus vasculopathy), thrombotic microangiopathy (that can be associated with hemolytic uremic syndrome or thrombotic thrombocytopenic purpura, or antiphospholipid antibodies, or scleroderma/mixed connective tissue disease), and necrotizing vasculitis. In addition, "lupus podocytopathy" can also be seen in cases of severe proteinuria but without obvious glomerular alterations reminiscent of minimal change disease or focal segmental glomerulosclerosis, accompanied with or without mesangial deposits; therefore, LN can mimic almost every glomerular disease. Uncommonly, amyloidosis, fibrillary glomerulonephritis, other "nonlupus" nephritides, drug-induced LN, etc., have been reported.

According to Kudose et al. [59], five predominant features allow the distinction LN from other glomerular diseases: the full house pattern, intense C1q staining, extraglomerular deposits, combined subendothelial and subepithelial deposits, and endothelial tubuloreticular inclusions, with a high specificity and varying sensitivity.

Differential diagnosis includes glomerulonephritis with similar findings in light microscopy, but usually immunofluorescence examination (full house pattern), clinical history, and serology allow the distinction. Cryoglobulinemic glomerulonephritis is a major differential diagnosis, especially for class IV nephritis, since both can have a membranoproliferative pattern and "hyaline" deposits into glomerular loops, a situation complicating more by the fact that lupus can coexist with cryoglobulinemia or may show "organized" deposits by EM examination. In cryoglobulinemic glomerulonephritis, IgM usually predominates over other immunoglobulins, and there is no full house pattern in immunofluorescence, although exceptions have been described. In addition, EM examination may highlight structures of cryoglobulins in some cases. Furthermore, if necrosis and crescents predominate in histology without essential glomerular hypercellularity/proliferation, pauci-immune necrotizing vasculitis enters the differential diagnosis. Lupus serologies can provide important information in these cases, because sometimes in LN, antineutrophil cytoplasmic autoantibodies can be positive. Membranous nephropathy, especially in young women, should be examined carefully, since some cases may belong to lupus membranous. Serology may offer again some additional information, although sometimes the serology of lupus can be positive after years from the initial diagnosis of membranous. In these cases, a close follow-up is required.

In cases with mesangial proliferation with or without endocapillary proliferation, IgA nephropathy enters the differential diagnosis. Again, immunofluorescence examination will be the cornerstone for diagnosis. Notably, rheumatoid arthritis, a disease entity that can share common features with SLE, sometimes can be combined with IgA nephropathy, possibly due to rheumatoid factor related IgA. Uncommon glomerulopathies/glomerulonephritides, such as fibrillary or immunotactoid glomerulonephritis, may show mesangial expansion and positivity in immunofluorescence for IgG immunoglobulin, C3 complement component, or light chains. In these cases, EM examination has a pivotal role for diagnosis, by demonstrating the fibrils or microtubules accordingly. Interestingly, even uncommon diseases, such as fibrillary glomerulonephritis, have been described rarely in the literature, in the setting of LN. Podocytopathies, such as minimal change disease, have also been described in the context of SLE.

Rare cases of nonlupus nephritides with full house pattern in immunofluorescence examination mimicking LN have also been reported [60], including infection-related glomerulonephritis (such as endocarditis-related glomerulonephritis), cancer-associated membranous glomerulopathy, cryoglobulinemic glomerulonephritis, immune-complex-mediated glomerulonephritis lupus-like in HIV-infected patients, etc. If there is no convincing evidence of a specific etiology, the follow-up of the patients is required since some of these patients may develop positive lupus serology in the future.

However, even with the stringent criteria, rare examples of nonlupus glomerulopathies may exhibit characteristic features of LN. Furthermore, the ISN/RPS classification states that "it is important to realize that the kidney biopsy findings, per se, cannot be used to establish a diagnosis of SLE," requiring for this purpose a combination of clinical, serological, and histological data.

6. Management of lupus nephritis

The treatment of LN depends primarily on the histopathological findings of the kidney biopsy. Thus, not all histopathological classes need to receive immunosuppressive therapy. However, regardless of the need of immunosuppressive therapy, all patients with LN should be treated with antimalarial drugs, namely hydroxychloroquine [61].

6.1 Class I (minimal mesangial) and class II (mesangial proliferative)

Most patients with LN belonging to these two classes present with minor clinical findings, regarding kidney involvement. Their kidney function is normal, while they often present with mild subnephrotic proteinuria and/or microscopic hematuria. These patients have an excellent renal prognosis, and there is no reason to treat with immunosuppressive therapy [62] in the absence of extrarenal manifestations.

An exception is warranted for patients with nephrotic syndrome or nephrotic-range proteinuria, who have class I or II in histology. These patients probably have lupus podocytopathy. In this regard, electron microscopy is helpful to establish the diagnosis by demonstrating podocyte effacement. The usual treatment consists of oral prednisolone 1 mg/kg once daily (maximum dose of 80 mg) for one to four months followed by gradual tapering after achieving remission [63].

6.2 Class III (focal) and class IV (diffuse) lupus nephritis

Class III and IV LN is an aggressive disease that requires a quick and effective implementation of the therapeutic strategy. The therapeutic goal of patients with the above histological classes is the achievement of *complete response*, which translates to the recession of immunologic and inflammatory activity. The clinical criteria of defining a response to therapy are somewhat controversial and not universal, because a series of clinical studies and/or associations have defined different goals for a complete response. Nevertheless, all response criteria agree in the reduction of proteinuria and the improvement of the kidney function. We most commonly use the criteria published by the Improving Global Outcomes (KDIGO) Consensus Conference guidelines for glomerulonephritis, namely the reduction of proteinuria to <0.5 g/day measured by 24-hour urine collection or by the protein-to-creatinine ratio, the stabilization or improvement of the kidney function (±10% of the baseline) in a period of 6–12 months of therapy, as well the normalization of the urine sediment to red blood cells (RBCs) to ≤10 high-power field and absence of RBC casts [64]. Therapy must be initiated promptly after the acquisition of the diagnosis because a delay is related to irreversible kidney damage [65].

Traditionally, immunosuppressive therapy in patients with LN consists of two phases. The initial phase is the first phase with more intensive immunosuppressive, which usually lasts six months or until a remission is achieved. The second phase is a prolonged maintenance phase, which ensures the remission and the avoidance of a relapse [64]. With the most modern management of LN, we do not separate so strictly the two phases and we use an undivided approach, so that the duration of initial therapy varies; it can be as short as three months or as long as one year but averages approximately six months.

The immunosuppression of the initial phase includes two agents. The first one is always glucocorticoids combined with either mycophenolate mofetil (MMF) or

intravenous cyclophosphamide. There are a lot of commonly used dosing regimens for the glucocorticoids. We most commonly initiate the therapy with the administration of 0.5–1 mg/kg/day prednisolone (maximum dose 80 mg/day) followed by a gradual tapering at three to six months. When the clinical or histological findings are more severe (worsening of kidney function and crescents formation), then a therapeutic opening with intravenous daily pulses of 0.5–1 g methylprednisolone for three days is preferred [65, 66]. The use of intravenous cyclophosphamide was established as the standard of care in the 1980s after a series of trials evaluated its efficacy compared with monotherapy with glucocorticoids regarding the kidney prognosis and avoiding the development of ESKD [67]. The standard National Institute of Health (NIH) regimen consists of 0.5–1 g/m^2 monthly doses of intravenous cyclophosphamide for a period of six months [64]. The second option is the Euro-Lupus regimen, which consists of 500 mg intravenous cyclophosphamide every two weeks for a total period of three months, a remission-inducing regimen of low-dose IV cyclophosphamide (cumulative dose 3 g) that achieves clinical results comparable with those obtained with a high-dose regimen [68]. The alternative induction regimen consists of glucocorticoids plus MMF. The efficacy of this regimen compared with the one with cyclophosphamide was documented with the Aspreva Lupus Management Study (ALMS), where 370 patients with class III–V LN participated to open-label MMF (target dosage 3 g/day) or IV-cyclophosphamide (0.5–1.0 g/m^2 in monthly pulses) in a 24-week induction study. The study did not detect a significantly different response rate between the two groups: 104 (56.2%) of 185 patients responded to MMF compared with 98 (53.0%) of 185 to IV-cyclophosphamide. Moreover, no significant differences between the MMF and IV-cyclophosphamide groups with regard to rates of adverse events, serious adverse events, or infections were detected [69]. The dose of the MMF in this trial was 1.5 g twice daily. Enteric-coated mycophenolate sodium (EC-MPS) is an equivalent drug for patients who are unable to tolerate adequate doses of MMF due to gastrointestinal side effects (1 g of MMF is equivalent to 720 mg of EC-MPS). Although there are no clear guidelines regarding the selection of the initial induction therapy, MMF is preferred for younger patients with concerns about fertility since cyclophosphamide may adversely affect fertility. Nevertheless, in agreement with the EULAR recommendations, high-dose intravenous cyclophosphamide (0.5–0.75 g/m^2 monthly for six months) can be considered in patients with impaired renal function and/or histopathological factors [66]. The histopathological factors are included at the modified NIH activity index criteria, namely the endocapillary hypercellularity, karyorrhexis, fibrinoid necrosis, hyaline deposits, cellular/fibrocellular crescents, and interstitial inflammation [70].

Rituximab, which is a monoclonal antibody that targets the CD20 antigen and depletes the B cells, is not used as initial therapy based upon data from a randomized trial, where 144 patients with class III or class IV LN treated concomitantly with MMF, and corticosteroids were randomized 1:1 to receive rituximab (1000 mg) or placebo and where no statistically significant difference in rates of complete or partial remission was found [71]. Yet, a systematic review of observational studies and case reports showed favorable results for patients with LN resistant to the standard care of MMF or cyclophosphamide [72].

The use of tacrolimus as part of a "multitarget" regimen in combination with MMF or intravenous cyclophosphamide is based on a series of Chinese trials, where the response rate regarding the reduction of the proteinuria was higher using the multitarget regimen. Overall, these limited data are insufficient to support the use of tacrolimus as first-line initial therapy for severe LN, and more studies are needed [73].

In the past few years, a new drug, belimumab, which is an IgG1-lambda monoclonal antibody that prevents the survival of B lymphocytes by blocking the binding of soluble human B lymphocyte stimulator protein to receptors on B lymphocytes, which results to the reduction of the autoimmune response, has been emerged, and it will probably play a role in the initial phase of treatment. In a recent clinical trial involving patients with active LN, the addition of belimumab to the standard induction therapy (MMF or cyclophosphamide) showed that more patients who received belimumab had a primary efficacy renal response than those who received standard therapy alone [74]. A post hoc analysis of this study [75] showed that the effect of belimumab on kidney response, time to kidney-related events, or death was related to the histological type of kidney nephritis. Specifically, patients with class III or IV lupus nephritis were benefited by the addition of belimumab, while patients with class V lupus nephritis or mixed class lupus nephritis (III + V or IV + V) reaped no benefit by the addition of belimumab. It was also shown that patients with a greater degree of proteinuria (UPCR>3 g/g) do not respond to the addition of belimumab. These results constitute a first step toward a more personalized treatment of lupus nephritis.

During the second phase of LN treatment, the prevention of a relapse is the main goal [76]. The duration of maintenance therapy is three to five years [77]. The optimal therapy consists of MMF at a dose of 1000 mg twice daily. The ALMS Maintenance Trial proved that MMF was superior to azathioprine in maintaining a renal response to treatment and in preventing relapse in patients with LN who had a responded to initial therapy [78]. However, azathioprine is preferred for patients who want to become pregnant or for patients who cannot tolerate MMF. The dose of azathioprine is 2 mg/kg per day to a maximum of 150–200 mg/day. Low-dose oral prednisolone (0.05–0.2 mg/kg) is continued in most patients on maintenance therapy.

Patients with focal or diffuse LN resistant to initial therapy are treated with the alternative therapy. Patients resistant to CYC are switched to MMF, and patients resistant to MMF are switched to CYC [65]. In cases of a relapse, we most commonly treat patients with the same regimen that led to the initial remission. Concerns regarding the cumulative dose of CYC and the development of toxicity or infertility can lead sometimes to the alternative choice of MMF [79].

6.3 Class V (lupus membranous nephropathy)

The majority of patients with this histological class are presented with nephrotic syndrome or nephrotic-range proteinuria. Lupus patients with nephrotic syndrome due to membranous nephropathy should receive immunosuppression. Patients with nephrotic-range proteinuria despite the use of renin-angiotensin system blockers and/or patients with worsening of their kidney function should also receive immunosuppressive therapy [64, 80].

The general scheme consists of glucocorticoids plus either MMF or CYC or a calcineurin inhibitor or rituximab. All of the above treatments have shown comparable efficacy, although MMF probably is showing a better safety profile [69, 81]. Calcineurin inhibitors that is, cyclosporin or tacrolimus, should be given cautiously in patients with impaired kidney function considering its potential for nephrotoxicity. According to the KDIGO and the EULAR guidelines, MMF is a reasonable first line of choice in these patients. However, if MMF is proven ineffective, cyclophosphamide may be used for six months in an effort to induce long-term remission [82]. Long-term calcineurin inhibitor or rituximab may also be tried if the patient had prior significant exposure to cyclophosphamide or if there are other contraindications.

The dose of MMF and CYC is the same as for the treatment of class III and IV LN. Cyclosporine, when used, is started at 3–5 mg/kg/day in two divides doses and tacrolimus at 0.05–0.1 mg/kg/day in two divided doses. Consequently, we measure whole blood trough cyclosporine or tacrolimus levels, and 2 hours after receiving dose [C2] levels for cyclosporine to navigate through therapy. The desired trough levels range from 100 to 200 ng/ml for cyclosporine and 4–6 ng/ml for tacrolimus, whereas it is 600–800 ng/ml for C2 cyclosporine levels.

Patients who have concurrent lupus membranous nephropathy and focal or diffuse LN are treated with the same approach as used for those with focal or diffuse LN alone (**Table 2**) [64].

6.4 Class VI (advanced sclerosing lupus nephritis)

Class VI disease is characterized by global sclerosis of more than 90% of glomeruli. The immunosuppressive therapy is highly unlikely to benefit them, and it will only produce adverse effects. Hence, these patients need to be treated as chronic kidney disease to control the blood pressure, to reduce the proteinuria by using renin-angiotensin system blockers, and to prepare for the next step, when it is needed, the kidney replacement therapy.

6.5 General management

General supportive measures in all patients with LN, as with other patients with glomerulonephritis, include the restriction of dietary sodium intake to <2 g/day, the restriction of protein intake to 0.8 g/kg/day for patients with chronic kidney disease with a GRF < 60 ml/min/1.73 m^2, blood pressure control with a goal of <120–130/80 mmHg, the use of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker to maximally tolerated or allowed daily dose for the minimization of proteinuria and for the concomitant control of the blood pressure, the treatment of hyperlipidemia with lifestyle modifications (exercise, weight reduction, and smoking cessation), and the use of statins when needed, thrombosis prophylaxis for patients with nephrotic syndrome, and prophylaxis for *Pneumocystis jirovecii* pneumonia with trimethoprim/sulfamethoxazole, and the minimization of bone loss and osteoporosis prophylaxis due to the long-term glucocorticoid treatment [64].

6.6 Management of ESKD

Patients who develop ESKD can be managed with kidney transplantation, hemodialysis, or peritoneal dialysis. As with the other causes of ESKD, kidney transplantation is the best modality, with the best overall prognosis and survival, and so is preferred over hemodialysis or peritoneal dialysis [83]. A preemptive transplantation may be carried out when the extrarenal manifestations do not bear any contraindication for surgery [84]. The recurrence rate of LN at the kidney allograft was examined using the United Network for Organ Sharing files, and it was found in 2.4% (167 of 6780 patients) [85]. Among the patients who are on hemodialysis or peritoneal dialysis, there is no difference regarding the survival rates and mortality [86]. It must be noted, interestingly, that the development of ESKD and the initiation of a kidney replacement therapy are in the majority of patients associated with a complete or partial remission of the extrarenal manifestations of systemic lupus erythematosus [87].

Treatment	Dosage	Line of treatment	References
Cyclophosphamide (NIH)	0.5–1 g/m^2 monthly for six months	First line	KDIGO [64]
Cyclophosphamide (Eurolupus)	0.5 g every two weeks for three months	First line	Houssiau et al. [68]
Mycophenolate	3 g/day	First line	Appel et al. [69]
Glucocorticoids	0.5–1 mg/kg/day—tapering for three to six months	First line	Esdaile et al. [65]; Boumpas et al. [66]
Tacrolimus	4 mg/day	Part of multitarget therapy	Liu et al. [73]
Belimumab	10 mg/kg per 28 days	Added on regular therapy	Furie et al. [74]

Table 2.
Induction therapy of lupus nephritis class III, IV, III + V, or IV + V.

7. Prognosis of LN and risk factors for progression

The percentage of patients that achieve a complete remission within six months of therapy is 30% [88, 89]. Although the rates over the last decades have been becoming better, up to 20% of patients with LN will ultimately develop ESKD [90]. Thus, the ability to predict the long-term renal outcome is of vital importance. A better long-term prognosis is associated with attaining the complete response of active LN. What favors the long-term renal outcome is the early decrease of proteinuria levels over six months of treatment compared with patients with persistently high-grade proteinuria [91]. Probably, the most reliable predictor of good long-term renal outcome is proteinuria levels <0.7–0.8 g/day at one year after the initiation of treatment [92]. Regarding the demographic risk factors, Caucasians have the best prognosis and Africans the worst, whereas Asians have an intermediate prognosis. Black patients present worse outcomes with increased rates of ESKD and mortality [93]. The main clinical risk factors for the development of chronic kidney disease are baseline hypertension, nephrotic-range proteinuria, young age, anemia, and elevated serum creatinine at the time of biopsy [94]. There is a well-established link between histopathological findings on kidney biopsy and the clinical course of LN, with mesangial nephritis (class II) carrying the best renal prognosis while proliferative nephritis (classes III and IV) carrying the worst with a more aggressive course. Membranous (class V) nephritis is considered relative mild [45]. What is also very important are the high activity and chronicity indexes, which are independent predictors of ESKD [95]. To be more specific, cellular crescents, extracapillary proliferation, and interstitial fibrosis in the renal biopsy have the highest predictive value [95].

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Section 2

Cardiovascular Disease

Chapter 4

Accelerated Atherosclerosis in SLE: Mechanisms, Consequences, and Future Directions

Teresa Semalulu and Konstantinos Tselios

Abstract

The bimodal mortality rate in systemic lupus erythematosus (SLE) has been well documented, with atherosclerosis identified as a leading cause of late-stage death. Multiple mechanisms are responsible for accelerated atherosclerosis in SLE, ultimately resulting in endothelial dysfunction, arterial stiffness, arterial wall thickening, and plaque formation. This leads to an increased risk of coronary artery disease, cardiovascular events, cerebrovascular accidents, and peripheral arterial disease. SLE patients are not only impacted by traditional risk factors for cardiovascular disease (age, smoking, dyslipidemia, diabetes), but additionally nontraditional risk factors (prolonged corticosteroid use, disease activity and chronic inflammation). Identifying the impact of traditional risk factors and mediating nontraditional risk factors in SLE are vital to reduce morbidity and mortality related to atherosclerosis. SLE-specific screening methods should be established in the routine care of these patients, including the use of validated modified risk scores and imaging modalities. Furthermore, the utility of disease-specific biomarkers and anti-atherosclerotic therapies should be elicited. This chapter will provide an overview of considerations for the mechanisms, impact, and prevention of atherosclerosis in SLE patients.

Keywords: systemic lupus erythematosus, atherosclerosis, endothelial dysfunction, cardiovascular disease, coronary artery disease, cerebrovascular accident, peripheral arterial disease, risk stratification

1. Introduction

Survival in systemic lupus erythematosus (SLE) has dramatically improved over recent decades due to advancements in early diagnosis and therapies to prevent end-stage organ damage, particularly at the onset of disease [1, 2]. In 1976, Urowitz et al. reported a bimodal distribution of death in SLE, with atherosclerosis identified as a leading cause of late-stage mortality [3]. Although the prevalence and severity of the atherosclerotic cardiovascular events (CVEs) have been steadily decreasing over the last decades, the standardized mortality ratio (SMR) from atherosclerosis remains threefold higher compared with the general population [4].

Atherosclerosis is an inflammatory condition characterized by the storage of lipids and the accumulation of immune cells in the media layer of the arterial wall in medium- and large-sized arteries. Progressing disease will eventually lead to ischemia and hypoperfusion or complete obstruction of the blood flow in the affected organs, which manifests as CVEs, cerebrovascular accidents (CVA or stroke), and peripheral arterial disease (PAD) [5–8]. SLE patients have an earlier onset of atherosclerosis compared with the general population, which is not completely explained by traditional risk factors [9]. SLE-related disease factors are felt to contribute substantially to premature and accelerated atherosclerotic disease [10, 11]. The pathophysiology of accelerated atherosclerosis is not completely understood, but is a consequence of complex interactions between autoimmunity, chronic inflammation, vascular repair, traditional risk factors, and medications [12, 13].

Focused efforts by clinicians must incorporate preventative strategies to reduce the impact of traditional and nontraditional cardiovascular risk factors in SLE patients. This chapter provides an overview of considerations for the mechanisms, impact, and prevention of atherosclerosis in SLE.

2. Mechanisms

Traditional and nontraditional risk factors impact the risk of atherosclerotic disease in SLE patients [4, 14]. Traditional risk factors include: (a) non-modifiable risk factors (age, sex, and family history of atherosclerosis) and (b) modifiable risk factors (hypertension, diabetes, dyslipidemia, smoking, metabolic syndrome, elevated homocysteine levels, etc.). Lupus-related (nontraditional) risk factors include disease activity and related damage, disease duration, autoantibodies, soluble inflammatory mediators, disease-specific phenotypes, and comorbidities as well as select medications [4]. The aforementioned factors are shown in **Table 1**. In most cases, several of these factors act simultaneously to accelerate atherosclerosis; hence a comprehensive approach for cardiovascular risk reduction is warranted.

2.1 Traditional non-modifiable risk factors

Age: Age over 48 and postmenopausal status are independent risk factors of CVEs (HR 1.04–5.1) [15]. Subclinical markers of atherosclerosis (i.e., endothelial dysfunction, arterial stiffness, arterial wall thickening and/or plaque formation, coronary artery calcification, and angiographically defined plaques) are associated with increasing age [4].

Sex: Male sex is a predictor of CVEs (HR 1.56–6.2) and subclinical atherosclerosis [4].

Family history: A positive family history of coronary artery disease (CAD) is defined as the occurrence of a CVE in a first-degree male relative aged 55 years or younger, or a first-degree female relative aged 65 years or younger. Family history is associated with increased risk of CVEs, though this was not associated with subclinical disease [4].

2.2 Traditional modifiable risk factors

Hypertension: The prevalence of hypertension in SLE ranges from 25 to 74%, which is likely related to renal disease, chronic nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoid use [4]. Moreover, the activation of the

Traditional risk factors	
Non-modifiable	Age
	Male sex
	Family history
Modifiable	Arterial hypertension
	Diabetes
	Dyslipidemia
	Smoking
	Metabolic syndrome
	Elevated homocysteine
Nontraditional risk factors	
	Disease activity
	Cumulative disease-related damage
	Disease duration
	Disease phenotypes (e.g., neuropsychiatric disease, renal disease, leukopenia, lymphopenia)
	Autoantibodies (e.g., anticardiolipin, anti-dsDNA)
	Soluble inflammatory mediators (e.g., high-sensitivity C-reactive protein)
	Select therapies (e.g., high dose glucocorticoids, azathioprine)
	NSAID use
	Vitamin D deficiency

Table 1.
Risk factors for atherosclerotic disease in systemic lupus erythematosus.

renin-angiotensin system, increased levels of endothelin-1, and oxidative stress along with certain cytokines (IL-6, IL-17, TNFa) play a significant role [16]. Hypertension is an independent risk factor for CVEs (RR 1.05–3.5) [4]. Blood pressure in SLE has been found to fluctuate significantly, thus time-adjusted mean systolic and diastolic blood pressure may capture the cardiovascular risk in SLE patients more accurately than traditional definitions of blood pressure [17]. It was recently shown that levels of blood pressure between 130 and 139 mmHg (for systolic blood pressure) and between 80 and 89 mmHg (for diastolic blood pressure) confer a significantly higher risk for CVEs compared with blood pressure levels of <130/80 mmHg [18].

Diabetes: In SLE, diabetes is an independent risk factor for CVEs and subclinical disease detected by carotid intima-media thickness (IMT) and myocardial perfusion defects [4]. Insulin resistance in diabetic and non-diabetic SLE patients is less frequently related to glucocorticoid use, but is attributed to disease activity, elevated inflammatory markers, and increased oxidized LDL [19]. Impairment of glucose metabolism has been demonstrated by decreased sensitivity to insulin in non-diabetic lupus patients. Euglycemic state is achieved by a compensatory increase in insulin secretion [4].

Dyslipidemia: Dyslipidemia in SLE is believed to be secondary to autoantibody production against lipoprotein lipase (LPL), oxidized low-density lipoproteins (LDL), high-density lipoprotein (HDL), and apolipoprotein A1 [4]. There is also increased hepatic synthesis of very low-density lipoproteins (VLDL) related to cytokine release [20]. The first pattern of dyslipidemia in SLE is reflective of active or untreated disease, with increased triglycerides (TG) and VLDL as well as decreased HDL. The second pattern is related to renal disease, hypothyroidism, and glucocorticoid use and is characterized by elevated total cholesterol (TC), TGs, and LDL [4]. Decreased HDL, increased TGs and TC levels are independent risk factors for CVEs [4, 17, 20, 21].

Recently, the role of proinflammatory HDL in accelerated atherosclerosis in SLE was described. It is believed that chemically modified HDL molecules lose their antiatherogenic properties and induce vascular inflammation through immune-mediated mechanisms. Proinflammatory HDL was strongly associated with increased carotid IMT and plaque formation [22]. Dysfunctional proinflammatory HDL confers increased risk for atherosclerosis in women with SLE [22].

Smoking: Smoking is an independent predictor of CVEs (HR 2.2–3.7) and is associated with subclinical disease identified by carotid plaque and coronary artery calcification (CAC) [4].

Metabolic syndrome: Metabolic syndrome ("abnormal" waist circumference with elevated triglycerides, arterial hypertension, impaired glucose metabolism, and decreased HDL levels) is an independent risk factor for cardiovascular mortality and may better represent cardiovascular risk in females, rather than obesity [23]. Patients with SLE are three times more likely to have metabolic syndrome compared with the general population [24]. Metabolic syndrome has been associated with increased carotid IMT, arterial stiffness, and CAC [4]. Obesity seems to be the primary risk factor in such patients. Lupus patients with BMI > 30 demonstrated endothelial dysfunction, increased carotid IMT and plaque formation (HR 1.06–6.16), and CAC [4]. Obesity has also been recognized as the major driver of accelerated atherosclerosis in pediatric lupus patients, as assessed prospectively by IMT progression [25].

Elevated homocysteine: Elevated homocysteine levels are related to CAC and increased carotid IMT or plaques [4]. Elevated homocysteine levels increase oxidative stress and inhibition of endothelial derived nitric oxide synthetase, causing endothelial dysfunction. Homocysteine may also induce a prothrombotic state by impairing the function of platelets and soluble coagulation factors [26].

2.3 Nontraditional (lupus-related) risk factors

Disease-related factors: SLE is an independent predictor of CVEs due to various aspects of the disease. Disease-related factors independently associated with CVEs are disease activity (HR 1.05–1.2), as measured by the SLE Disease Activity Index (SLEDAI), disease-related damage, as measured by the Systemic Lupus International Collaborating Clinics (SLICC) Damage Index (HR 1.3–4.1), and disease duration (HR 1.10–1.45) [4].

SLE phenotypes and comorbidities: SLE patients with renal and neuropsychiatric disease are at increased risk of CVEs. Renal impairment (HR 1.2–6.8) and proteinuria (HR 2.4) are independent risk factors of CVEs. Renal impairment and lupus nephritis are also associated with carotid IMT and plaque, and increased aortic stiffness. Neuropsychiatric disease is associated with CVEs (HR 2.2–5.2). Depression and bone mineral density were associated with increased CAC, while leukopenia was associated with increased aortic stiffness and lymphopenia with CVE and progression of carotid IMT [4].

Autoantibodies: Several autoantibodies are associated with clinical and subclinical cardiovascular disease, including anticardiolipin antibodies (aCL), anti-β2 glycoprotein 1 (GPI) antibodies, lupus anticoagulant, and anti-dsDNA antibodies. Presence of aCL (HR 3.1–5.8), GPI (HR 5.2), lupus anticoagulant (HR 1.74), and anti-dsDNA (HR 1.56) are independent predictors of CVEs.

Both aCL and lupus anticoagulant are associated with carotid plaques and coronary calcifications, anti-b2GPI antibodies are associated with coronary calcifications, and anti-dsDNA antibodies with non-calcified coronary plaques. Other phospholipid

epitopes, such as anti-oxPAPC (oxidized palmitoyl arachidonoyl phosphocholine), are risk factors for carotid IMT and plaque formation (HR 1.06). Anti-Sm antibodies are protective against carotid plaques [4].

Soluble inflammatory mediators: High-sensitivity C-reactive protein (hsCRP) independently predicts CVEs (HR 1.6–3.4), endothelial dysfunction, arterial stiffness, carotid IMT, and plaque, as well as CAC scores. Complement fragment C3 is associated with increased arterial stiffness, carotid IMT, and CAC [4]. Tumor necrosis factor (TNF)-like inducer of apoptosis increased the risk of carotid IMT and plaque by almost 30-fold, while TNF-α, vascular cell adhesion molecule (VCAM), E-selectin, and intercellular adhesion molecule 1 (ICAM-1) were associated with CAC. Additional inflammatory mediators found to be associated with clinical and subclinical atherosclerotic disease include low transforming growth factor-β (TGF-b), type I interferons, adipocytokines, leptin, and uric acid [4].

Select therapies: The use of high-dose glucocorticoids independently predicts CVEs (HR 2.5), carotid IMT and plaque formation, CAC, and arterial stiffness. Azathioprine (HR 1.45) and the general use of immunosuppressive agents (HR 1.7) were associated with CVEs, while hydroxychloroquine is protective (HR 0.77) [4].

Other risk factors for atherosclerosis that have been identified, including NSAID use and vitamin D deficiency [14].

2.4 Immunopathophysiology of atherosclerosis in SLE

The interplay of the traditional and disease-related risk factors results in the activation of the endothelial cells that express high levels of adhesion molecules such as ICAM-1, VCAM, and E-selectin. In parallel, there is increased apoptosis of the endothelial cells that is mediated through Fas/FasL and TNF/TNFRII interactions, while its potency leads to insufficient apoptotic debris clearance from monocytes/macrophages. At the same time, IFN-a, a major pathogenetic cytokine in SLE, induces dysregulation of the endothelial progenitor cells that leads to impaired endothelial repair [27].

The proinflammatory cytokine milieu in SLE as well as the increased oxidative stress (expressed with increased levels of reactive oxygen species, ROS) augments the oxidation of LDL. Under normal circumstances, HDL inhibits this pathway effectively. However, in SLE, a certain proportion of the HDL molecules are proinflammatory. At the tissue level (atherosclerotic plaque), oxidized LDL (oxLDL) activates the endothelial cells. This, along with the overexpression of adhesion molecules, induces the subepithelial recruitment of monocytes/macrophages that will eventually phagocytose the oxLDL molecules and other lipids and will transform to "foam" cells [27].

Abundant numbers of neutrophils and plasmacytoid dendritic cells (DCs) have also been detected within the plaque. Neutrophils release neutrophil extracellular traps (NETs) that induce endothelial damage and activate the macrophages toward the production of IL-1β, TNFα, and MCP-1. Plasmacytoid DCs and low-density granulocytes secrete IFN-a, which induces platelet activation. Moreover, B cells are producing antibodies against oxLDL and b2GPI, a potent anticoagulant protein; the formed immune complexes will accelerate the rate of "foam" cell generation and enhance IFNa secretion from the DCs. Simultaneously, the immune complexes containing oxLDL and/or anti-b2GPI and other phospholipid epitopes bind to the C1q receptor of the endothelial cells and induce the expression of VCAM-1, resulting in an auto-amplification loop [27].

Certain T cell subpopulations are also involved in the atherogenic process, mainly Th17 and Th1, while T regulatory cells (Tregs) are found in reduced numbers in the periphery and in the vessel wall. Both Th1 and Th17 cells contribute to the perpetuation of inflammation by secreting proinflammatory cytokines such as Il-17. This has been associated to increased vulnerability of the atherosclerotic plaques that may result in platelet aggregation and thrombosis. All these mechanisms are poorly regulated by Tregs, which are quantitatively and qualitatively impaired in SLE. Tregs may suppress the principal effectors of arterial wall inflammation, namely Th1 and Th17 cells, and downregulate IFN-a and TNF-α. This action is mediated by IL-10 and TGF-β, by cell-to-cell contact mechanisms (including CTLA-4, cytotoxic T cell antigen 4), and by modulation of DC function. Tregs are also able to steer macrophage differentiation toward the M2 anti-inflammatory phenotype by downregulating CD36 and scavenger receptor A (SRA). This mechanism reduces the uptake of oxLDL, thus inhibiting foam cell formation [27].

Apart from the local effects, various cytokines have been shown to affect other risk factors. TNF-α induces a dyslipidemic profile with increased TG, decreased HDL, inhibition of lipoprotein lipase, and induction of VLDL synthesis. Serum levels of TNF-α are strongly related to disease activity and drive the activation of endothelial cells, smooth muscle cells, and macrophages, thus augmenting the atherogenic process. TNF-α is also implicated in endothelial cell apoptosis (through p55 receptor) and vulnerability of the atherosclerotic plaque. Low levels of the transforming growth factor β (TGF-b) in SLE are associated with the breakdown of immune tolerance and have demonstrated a strong correlation with premature atherosclerosis. Other cytokines that were shown to increase CV risk in lupus patients are tumor necrosis factor-like weak inducer of apoptosis (TWEAK), IL-6, vascular endothelial growth factor (VEGF), and type I interferons. Soluble CD40 ligand (sCD40L) is overexpressed in SLE and associated with increased activation of the endothelial cells through CD40 binding on their surface. It induces the coagulation cascade through the increase of tissue factor (TF) expression and is also related to plaque vulnerability. Increased sCD40L is associated with increased risk for recurrence after an acute coronary syndrome [27].

3. Consequences

Accelerated atherosclerosis has a significant impact on long-term morbidity and mortality in SLE. Resultant endothelial dysfunction, increased arterial wall thickening and stiffness, and plaque formation increase the risk of CVD, which is the most common cause of death in SLE [4, 28–31]. Additional consequences include increased PAD, CVA, and premature mortality [8, 32]. From 1970 to 2004, the University of Toronto Lupus Clinic documented a 10.9% (95% CI 9.0%–12.3%) prevalence of atherosclerotic vascular events (i.e., myocardial infarct [MI], angina, TIA, stroke, peripheral vascular disease, and sudden death presumed to be of cardiac etiology) among patients within the first 9 years of SLE diagnosis [33].

3.1 Cardiovascular disease

SLE is an independent risk factor for the development of CVD, providing similar cardiovascular risk as type 1 diabetes [34]. Numerous studies have demonstrated an increased risk of CVEs in SLE patients, which disproportionately impacts

premenopausal women [35–38]. Women (aged 35–44) with SLE followed at the University of Pittsburg Medical Center were 52 times more likely to have an MI (rate ratio 52.43, 95% CI 21.6–98.5), compared with healthy controls from the Framingham Offspring Heart Study [35]. Premenopausal women with SLE were two times as likely to be hospitalized from acute MI (proportionate morbidity ratio [PMR] 2.27, 95% CI 1.08–3.46) and almost four times more likely to be hospitalized for congestive heart failure (CHF) (PMR 3.80, 95% CI 2.41–5.19) [36], compared with age-matched controls. In a retrospective population-based study, SLE patients had an almost four times higher odds (OR 3.8, 95% CI 1.8–8.0) of being diagnosed with CVD within 2 years of their SLE diagnosis [37].

The increased burden of premature CVD is paired with worse overall outcomes. In a nationwide American study of almost 700,000 patients from 1993 to 2002, SLE patients had a higher probability of prolonged hospitalization following an acute MI (OR 1.46, 95% CI 1.31–1.61) compared with diabetic patients (OR 1.17, CI 1.16–1.19) and controls, when adjusted for age, sex, race/ethnicity, income, and CHF [39]. Adjusted in-hospital mortality was also greater for SLE patients (OR 1.68, 95% CI 1.43–2.04) compared with diabetic patients (OR 1.00, 95% CI 0.97–1.02) [39]. CVD remains the leading cause of mortality in SLE [28–30, 40].

3.2 Cerebrovascular accident

The prevalence of CVA in SLE has been reported as between 2 and 19% [41]. The risk of CVA in SLE is approximately 2–3-fold higher than the general population [42–46]. In a meta-analysis of stroke in SLE, 10 studies identified a 2.5-fold higher risk of stroke from all causes (RR 2.53, 95% CI 1.96–3.26), ischemic stroke (2.10, 95% CI 1.68–2.62), intracerebral hemorrhage (2.72, 95% CI 2.15–3.44), and subarachnoid hemorrhage (3.58, 95%CI 3.20–4.64). The greatest risk was among those aged 50 years or younger [43]. Standardized incidence ratios (SIRs) were 2.02 (95% CI 1.30–3.81) among SLE patients in a Chinese study [44]. Younger patients were disproportionately impacted, with the highest incidence ratios among ages 30–40 (SIR 21.0, 95% CI 7.84–56.5) and less than 30 years (SIR 22.8, 95% CI 5.67–91.7). Patients less than 30 years had a 54 times higher incidence of ischemic stroke (SIR 53.9, 95% CI 7.47–389), the highest among all age groups [44]. SLE patients are at highest risk of ischemic stroke and intracerebral hemorrhage [43, 44, 47]; this risk does not appear to be impacted by the development of end-stage renal disease in the context of lupus nephritis [48].

Premenopausal SLE patients are two times more likely to be hospitalized due to stroke (PMR 2.05, 95% CI 1.17–2.93), though a difference in hospitalization has not been consistently identified [44]. Moreover, lupus patients are at a higher risk of death from CVA compared with the general population, with strokes accounting for up to 15% of deaths in SLE [42, 49, 50].

3.3 Peripheral arterial disease

Peripheral arterial disease is often asymptomatic, and the ankle-brachial index (ABI) is typically used to assess for subclinical disease [51]. The prevalence of PAD in SLE has been reported between 21 and 33% [52–54]. SLE patients are four times more likely to have PAD (OR 3.9, 95% CI 1.8–7.9), compared with controls [54]. A retrospective review of the Taiwan National Health Insurance program data identified a ninefold higher risk of PAD (HR 9.39, 95% CI 7.70–11.5) in SLE patients, compared with controls [32]. Among this cohort, the greatest risk of PAD was within

the first year following diagnosis of SLE. Females had a higher risk compared with sex-matched controls (HR 9.90, 95% CI 7.98–12.3), than males (HR 5.96, 95% CI 3.50–10.2). Like other forms of vascular disease, the risk was highest among young patients (HR [for age < 34] 43.4, 95% CI 24.5–76.9) and declined over time [32].

Morbidity from symptomatic PAD can be substantial, as it may lead to disability and ischemic-related complications [55, 56]. Fortunately, the prevalence of symptomatic PAD seems to be substantially lower (1–2%) than asymptomatic disease in SLE [52, 57]. PAD is a predictor of all-cause mortality, cardiovascular disease, cardiovascular mortality, and stroke [57, 58].

3.4 Mortality

The bimodal distribution of death in lupus was first identified by Urowitz et al. in 1976, with atherosclerotic heart disease and infection most responsible for late-stage mortality [3]. Survival has significantly improved since the 1950s, as the 5-year and 10-year survival rates are greater than 92% in SLE, primarily due to advancements in therapy [2, 59]. Data from the Toronto Lupus Clinic, from 1971 to 2013, showed an improvement in mortality related to atherosclerosis from 1980–1989 (SMR 8.3, 95% CI 3.8–12.8) to 2010–2013 (SMR 3.2, 95% CI 0.1–6.3) [1]. The next leading causes of death were malignancy (SMR 1.4, 95% CI 0.2–2.7) and infection (SMR 0.9, 95% CI 0–1.9) [1]. Atherosclerosis has persistently been identified as the leading cause of death in SLE [1, 60].

4. The role of imaging modalities in atherosclerosis in SLE

Vascular imaging has been used in the general population to assess for atherosclerotic burden [26]. Carotid ultrasound with IMT and carotid plaque has been shown to independently predict CVEs. Various other imaging modalities have shown benefit in the general population, with yet unclear clinical value in the setting of SLE [26].

Flow-mediated dilation (FMD) of brachial artery: The initial stage of atherosclerosis is endothelial dysfunction, which can be assessed by FMD [61]. Impaired FMD has been shown to independently predict future CVE in the general population [62]. The generalizability of these findings is unclear in SLE [63]. A meta-analysis of 22 studies found a reduction in FMD in SLE patients, compared with controls [64]. FMD was also associated with traditional and disease-related cardiovascular risk factors and inversely related to carotid IMT. SLE was identified as a risk factor for impaired FMD [4].

Pulse-wave velocity (PWV): PWV analysis and the derivative variable augmentation index are surrogate measure of arterial stiffness, which occurs in the next stage of atherosclerosis [26, 65]. These are independent predictors of CVEs in the general population. Cross-sectional studies in SLE have found increased PWV to be related to traditional and disease-related risk factors, though the predictive value of PWV for future CVEs has not yet been tested in SLE [26].

Carotid intima-media thickness (IMT) and carotid plaque: During later stages of atherosclerosis, increased carotid IMT and plaque formation occur [4, 66]. This is characterized by limited reversibility potential. Mean carotid IMT measurements in asymptomatic SLE patients range from 0.37 mm to 0.89 mm, with increased carotid IMT independently associated with future CVEs (HR 1.35 after 8 years) [67–69]. Carotid IMT is also strongly associated with traditional and disease-related risk factors for cardiovascular disease in SLE [4].

Plaque detection in SLE ranges from 7 to 50%. Carotid plaque was found to more accurately predict CVEs in the general population, with the presence of both carotid and femoral plaques as a better predictor of CVEs than carotid plaques alone [26]. SLE patients with carotid plaques have more than a fourfold increased risk of CVE. One study showed that total plaque area was more strongly associated with clinical CAD than carotid IMT (HR 9.55 vs. 2.02, respectively) [69].

Coronary artery calcification (CAC): CAC measures atherosclerotic calcification [70]. Cardiac risk stratification can be accomplished by evaluating CAC, measured by the Agatston score. The prevalence of CAC has been reported between 7 and 48%, and CAC has been correlated with traditional and disease-related risk factors [4, 71, 72]. SLE is an independent predictor of CAC presence (RR 7.7–7.9) [71, 72]. One study demonstrated that non-calcified coronary plaques, which are prone to rupture, were detected in essentially all patients with CAC (45/47, 96%) and more than half of those without CAC (52/99, 53%). The presence of these plaques was related to age and anti-dsDNA antibodies [4].

Coronary angiography: A large prospective cohort study assessing the burden of atherosclerotic disease among SLE and non-SLE patients used coronary angiogram, the "gold standard" to assess flow limiting disease [26]. The rates of obstructive CAD were similar among SLE patients and controls (52% vs. 62%, $p = 0.11$), and SLE was an independent predictor of CAD (OR 2.24, 95% CI 1.08–4.67) [73]. However, SLE patients were younger than controls (mean age 49 vs. 70 years, $p < 0.001$), were less likely to have diabetes (14 vs. 35, $p < 0.001$) and/or hyperlipidemia (30 vs. 50, $p = 0.001$), and more likely to be on glucocorticoids (50 vs. 11, $p < 0.001$) [73]. Another study found postmenopausal state, hypertension, and the number of traditional cardiovascular risk factors to be associated with more severe angiographic abnormalities [74].

Myocardial perfusion evaluation with single-photon emission computed tomography (SPECT): Myocardial evaluation with SPECT is a reliable assessment of myocardial perfusion in the general population, with perfusion defects associated with an almost fourfold increased risk of MI and cardiac death [75]. An association between perfusion defects with traditional and disease-related risk factors has been identified in SLE studies. Myocardial perfusion defects are predictive of CAD (HR 12.0, 95% CI 2.8–60.1) [76]. However, SPECT may overestimate the burden of atherosclerotic disease in SLE, when compared with coronary angiogram [77].

Cardiac magnetic resonance imaging (MRI): Cardiac MRI has known predictive ability in the general population, with an increased incidence of MI and cardiovascular death [26]. Allowing visualization of microvascular disease, limited data suggest that perfusion defects may be relatively frequent in SLE patients in the absence of obstructive CAD [78]. Ventricular wall abnormalities may be better identified with cardiac MRI compared with conventional transthoracic echocardiogram [79]. A diffuse pattern of coronary artery wall contrast enhancement, reflective of vascular inflammation, is seen in SLE patients, compared with the patchy distribution seen in traditional CAD [4, 80].

Refer to **Table 2** for an overview of surrogate atherosclerotic measures in SLE.

5. Management of cardiovascular risk in SLE

Considerations for cardiovascular risk reduction in patients with SLE include the management of traditional and nontraditional atherosclerotic risk factors through

Imaging modality	Purpose	Associated traditional and disease-related cardiovascular risk factors
Flow-mediated dilatation (FMD)	Noninvasive assessment of endothelial dysfunction	Age, BMI > 30 Arterial hypertension Low HDL oxLDL
Pulse-wave velocity (PWV)	Noninvasive assessment of arterial stiffness	Age Male sex, BMI > 30 Arterial hypertension Diabetes, Elevated triglyceride Metabolic syndrome
Carotid intima-media thickness (IMT) and carotid plaque	Noninvasive measure of the presence of carotid plaques	Age Family history Male BMI > 30 Waist-to-hip ratio Arterial hypertension Diabetes Elevated total cholesterol Elevated LDL Low HDL or proin-inflammatory HDL Metabolic syndrome Elevated homocysteine, smoking
Coronary artery calcification (CAC)	Noninvasive measure of atherosclerotic calcification, as per Agatston score	Age Male sex BMI > 30 Arterial hypertension Diabetes Elevated total cholesterol Elevated triglycerides Metabolic syndrome Elevated homocysteine Smoking
Coronary angiography	Invasive "gold standard" assessment of flow limiting disease	Age Male sex Arterial hypertension Elevated total cholesterol Elevated HDL
Myocardial perfusion evaluation with single photon emission computed tomography (SPECT).	Noninvasive assessment of myocardial perfusion	Arterial hypertension Diabetes Elevated total cholesterol Elevated HDL
Cardiac Magnetic Resonance Imaging (MRI)	Noninvasive measurement of microvascular disease	-

Adapted from Tselios K, Sheane BJ, Gladman DD, Urowitz MB. Optimal monitoring for coronary heart disease risk in patients with systemic lupus Erythematosus: A systematic review. J Rheumatol. 2016;43(1):54–65.

Table 2.
Surrogate atherosclerosis measures in systemic lupus erythematosus.

screening and preventative strategies. The management of traditional risk factors and disease activity has been shown to significantly reduce atherosclerotic vascular events (HR 0.40, 95% CI 0.23–0.70), including angina, MI, TIAs, stroke, and CHF [81]. Given the lack of SLE-specific risk reduction approaches, the identification and management of modifiable risk factors remain the most effective means of reducing cardiovascular risk in lupus patients [59].

5.1 Risk reduction

5.1.1 Risk scores

Cardiovascular risk scores are used in the general population to estimate future risk of a cardiovascular event [82]. These scores are not completely generalizable to SLE patients, as they are generally validated in older patient populations than those affected by SLE, and do not take into account the impact of chronic systemic inflammation, which plays a major role in increasing atherosclerotic risk in these patients [4, 83]. In fact, the Framingham risk score (FRS) has been shown to largely underestimate cardiovascular risk in SLE [9]. After controlling for traditional risk factors in 296 SLE patients, there was a significantly higher risk of nonfatal MI (RR 10.1, 95% CI 5.8–15.6), death due to CVD (RR 17.0, 95% CI 8.1–29.7), overall CVD (RR 7.5, 95% CI 5.1–10.4), and stroke (RR 7.9, 95% CI 4.0–13.6) [84]. Urowitz et al. determined that the use of a modified FRS, which multiplies each item by 2, can more accurately predict cardiovascular risk in SLE [85].

The Systemic Coronary Risk Evaluation (SCORE) has been recommended by EULAR to calculate 10-year CVD risk in SLE [86]. Although SCORE has been shown to predict increased carotid IMT, its use in SLE is unclear as it likely also underestimates cardiovascular risk in SLE patients [4, 11, 86]. The Predictors of Risk for Elevated Flares, Damage Progression, and Increased Cardiovascular Disease in Patients with SLE (PREDICTS) score incorporates biomarkers in risk calculations and has previously been proposed as an alternative risk prediction score [83, 87].

5.1.2 Screening guidelines

As part of best practices, the Canadian Rheumatology Association (CRA) states that a cardiovascular risk assessment should be performed in newly diagnosed adult SLE patients [88]. A strong recommendation was made to initially and periodically assess for traditional risk factors (i.e., obesity, arterial hypertension, diabetes, dyslipidemia, and smoking) according to recommendations in the general population. There is also a conditional recommendation against the use of carotid ultrasonography for cardiovascular risk assessment except in select circumstances where expertise is available, since there is a high risk of false-positive results outside of the appropriate setting [88].

The *EULAR* recommendations for cardiovascular risk management in rheumatic and musculoskeletal diseases proposed several recommendations for the management of cardiovascular risk in SLE patients [89]. Cardiovascular risk modification should be guided by traditional and disease related risk factors. A blood pressure target of <130/80 should be considered, and ACE inhibitors or ARBs are recommended in lupus nephritis in patients with arterial hypertension or a urine protein-to-creatinine ratio > 500 mg/g [4]. Low disease activity, the lowest possible glucocorticoid dose and the use of hydroxychloroquine are recommended to reduce cardiovascular

risk. Aspirin should be used based on individual cardiovascular risk profile, and no immunosuppressive medications are recommended to lower risk of CVEs. Lipid management should be guided by general recommendations.

Others have also proposed annual assessments of smoking status and body mass index, routine diabetes screening, possible annual homocysteine levels, and hsCRP at each visit [4, 59]. Additional recommendations include carotid IMT and plaque assessments in patients with more than one traditional risk factor, postmenopausal status, or renal impairment [4].

5.1.3 Pharmacologic intervention

To date, hydroxychloroquine (HCQ) is the only immunomodulatory therapy recommended for cardioprotective benefit in SLE [89]. HCQ is an antimalarial with multiple mechanisms of action resulting in immunomodulatory and cardioprotective effects [59, 90]. It modifies the intracellular pH to block T-cell proliferation, inhibits toll-like receptor (TLR) activation, and reduces the production of select cytokines (i.e., TNF-alpha, IL-17, IL-6, IFNα, and IFNγ) [90]. HCQ also modifies antibody and self-antigen presentation and reduces oxidative stress. Furthermore, HCQ effectively reduces platelet aggregation, lipid levels, and insulin resistance, all mechanisms that are cardioprotective [90].

HCQ has been shown to consistently reduce SLE disease activity and flares [79, 80] as well as protect against damage accrual using SLICC Damage Index in the Lupus in Minorities: nature versus nurture (LUMINA) study (HR 0.55, 95% CI 0.34–0.87). There is also evidence of mortality benefit (HR 0.62, 95% CI 0.39–0.99) in a multinational Latin American inception cohort [91].

A multivariate analysis showed benefit in reducing plaque burden (adjusted OR 0.49, 95% CI 0.21–1.12). Use of HCQ has also been associated with lower aortic stiffness in premenopausal women (partial R2 0.025, p = 0.032) and a significant reduction of thromboembolic events (OR 0.32, 95% CI 0.14–0.74) [92].

6. Future directions

6.1 Screening

To mediate the impact of accelerated atherosclerosis in SLE, it is essential to establish effective screening mechanisms to detect early disease. Validated risk prediction tools will enhance the accuracy by which clinical risk of cardiovascular disease is predicted among lupus patients [12]. Longitudinal studies are warranted to determine the utility of biomarkers and various imaging modalities (**Table 2**) to predict CVEs and subclinical cardiovascular disease in SLE [4, 59]. Other potential biomarkers that have proven association with atherosclerotic risk include IL-1, adipocytokines, and peroxidase [83, 93]. Focusing research efforts in these areas will allow for successful cardiovascular risk stratification and ideally intervention at reversible stages of disease [4, 59].

6.2 Antiatherosclerotic therapies in SLE

No immunomodulatory medications have been found to have a favorable impact on atherosclerotic disease processes in SLE, aside from hydroxychloroquine [89, 90].

In vivo studies with mycophenolate mofetil (MMF) have shown promising results in mouse models with atherosclerosis [94]. MMF may reduce cardiovascular mortality in renal transplant patients with diabetes and has been shown to reduce the development of carotid artery plaques in non-SLE patients, by decreasing T cell activation and increasing regulatory T cells [95, 96]. However, there was no improvement in subclinical cardiovascular disease in a small prospective cohort study [97]. Larger studies may be warranted to explore the utility of MMF for this indication [59]. Celastrol, an anti-neoplastic drug with anti-inflammatory properties, is another promising drug that has been shown to inhibit atherosclerotic pathways and reduce plaque in animal models [93].

Biologic disease-modifying therapies (bDMARDs) should be further investigated. Hu et al. found a reduced risk of MI (OR 0.74, 95% CI 0.63–0.87), cardiovascular death (OR 0.62, 95% CI 0.40–0.95), and a composite endpoint of MI, stroke, and cardiovascular death (OR 0.69, 95% CI 0.53–0.89) in those on bDMARDs, compared with those not on bDMARDs [98]. These finding were mostly driven by the reduction of risk in rheumatoid arthritis patients, thus the role in SLE is unclear.

Interleukin-1β is a potent inflammatory cytokine that induces the production of IL-6, which is known to be associated with vascular events [91]. Canakinumab is an anti-IL-Iβ therapy that has been investigated as a potential antiatherosclerotic intervention in the general population. The Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS) is a randomized, double-blind, placebo-controlled trail that examined the impact of Canakinumab on adverse CVEs in patients with a previous history of MI and persistently elevated CRP (greater than 2 mg/L) [99]. Participants receiving Canakinumab 150 mg subcutaneously every 2 weeks had significantly less adverse CVEs (HR 0.86, 95% CI 0.75–0.99, $p = 0.031$) and hospitalization due to urgent revascularization for unstable angina (HR 0.83, 95% CI 0.73–0.95, $p = 0.005$). These results were all independent of lipid lowering effects. Post hoc analysis found that patients with less inflammation (defined as IL-6 below 1.65 ng/L) had a reduction in major adverse CVEs (HR 0.68, 95% CI 0.56–0.82) and cardiovascular mortality (HR 0.48, 95% CI 0.34–0.68) [100]. This study may not be generalizable to SLE patients since patients with known immunocompromised states or those already on systemic anti-inflammatory treatments were excluded. Moreover, Canakinumab may be cost prohibitive in this setting. Regardless, the mechanistic implications of reducing cardiovascular risk in the absence of lipid lowering effects are encouraging.

We also wonder whether new biologics, such a Belimumab and Anifrolumab, may reduce CVEs by reducing nontraditional risk factors, specifically glucocorticoid use and disease-related damage. The role of additional therapies in mediating atherosclerotic pathways, such as type 1 interferons, seems promising [59, 101]. Future research should explore the impact of harnessing other inflammatory mediators or enhancing regulatory mechanisms.

6.3 Addressing disparities

Socioeconomic and racial and ethnic disparities in cardiovascular risk, outcomes, and mortality remain persistent, despite advancements in SLE morbidity and mortality over several decades. Low socioeconomic status has been associated with increased cardiovascular risk factors [102, 103]. Racial disparities in CVD, stroke, and CV mortality have been identified [39, 104, 105], though findings vary [103, 106, 107]. One study found African American SLE patients to be on average 10 years younger

than their Caucasian peers at the time of first hospital admission for cardiovascular disease [108]. The same conclusions were also made for Hispanic SLE populations (as compared with Caucasians). It should be mentioned that socioeconomic variables were not taken into account in this study [108]. In another relevant study of the LUMINA cohort, this difference could not be reproduced [109]. These disparities should be explored further, with an aim to mediate disproportionate risk among affected groups.

7. Conclusions

Atherosclerosis is the leading cause of death in SLE and is responsible for substantial morbidity related to cardiovascular events, cerebrovascular accidents, and peripheral arterial disease. SLE patients are at increased risk of atherosclerotic disease due to traditional and nontraditional risk factors (e.g., disease activity and long-term glucocorticoid use). Clinicians should be aware of the need to limit the impact of nontraditional risk factors in order to reduce the burden of atherosclerotic disease in SLE. Current risk prediction tools likely underestimate cardiovascular risk in this population, thus further studies are needed to validate their use in SLE. The utility of imaging modalities for the routine assessment of subclinical cardiovascular disease has not yet been established and should remain a research priority. Hydroxychloroquine remains a mainstay in SLE management, as it provides additional cardioprotective benefit. Significant improvements in SLE survival over recent decades were largely due to disease-modifying therapies. With morbidity and mortality now largely related to accelerated atherosclerosis, evidence-based preventative strategies should be implemented to establish further gains in survival moving forward.

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Section 3

Pathogenesis

Chapter 5

Lupus Genetics

Eleni Klimi

Abstract

Lupus erythematosus is an autoimmune disorder with an important genetic component. Studies in monozygotic twins have revealed a concordance rate of 50% indicating that environmental factors might play a significant role in the development of the disease. Genes that are implicated in the pathogenesis of lupus erythematosus include HLA, Interferon genes, complement genes, cytokine genes (TNF, IL-10, IL-1β, IL-17, IL-23), NF-κB genes, ITGAM gene, PPP2CA genes, SIAE genes, SLAMF molecules, PTPN22, BLK, BANK1, PD-1 and X-linked genes (AIRE gene and others). Epigenetic factors which alter only the expression but not the DNA structure may also interfere with the development of the disease.

Keywords: lupus erythematosus, interferon, complement, TNF, IL-10, IL-1β, IL-17, IL-23, NF-κB, ITGAM, PPP2CA, SIAE, SLAMF, PTPN22, BLK, BANK1, PD-1, X-linked genes, chronic cutaneous lupus erythematosus, neonatal lupus, subacute lupus erythematosus, chilblain lupus, TREX1 gene, epigenetics

1. Introduction

Autoimmunity occurs when a component of a certain tissue of the human body becomes immunogenic with consequent production of autoantibodies against it.

For induction of autoimmunity three conditions are required.

a. Self-antigen.

b. An inflammatory environment.

c. A genetic predisposition.

For the production of a self-antigen, two mechanisms are implicated. A part of an inflammatory agent, a virus, for instance, may have similarities with a component of human tissue and in this way it becomes immunogenic; this mechanism is called molecular mimicry – a mechanism quite commonly encountered in nature. Another mechanism is epitope spreading when fragments of damaged tissue during the inflammatory process become immunogenic. Stimuli that may induce an inflammation are multiple: microbes, viruses, chemicals, stress, etc. As all human beings are exposed to various agents very frequently, it is quite difficult to identify the initial moment autoimmunity occurs and the responsible factor [1].

2. Lupus erythematosus

Lupus is the prototype of autoimmune diseases with B-cell hyperactivity resulting in the production of anti-DNA autoantibodies and manifests with abnormalities of internal organs. Renal insufficiency, hemolytic anemia, arterial and venous thromboses are common in SLE. Skin eruptions may also be observed in patients with SLE. Females are more frequently affected with the disease female: male ratio 6-10:1. Prevalence of SLE is relatively low 1 in 2000, in general population. Despite this fact, SLE remains an important health care problem and is associated with a significant financial burden to the community because of the young age of the individuals suffering from the disease. A study of survival from 2000 to 2002 has shown that almost 4% of all patients hospitalized in New York AND Pennsylvania with lupus die [2, 3].

Lupus is a disease with a strong genetic component as it runs in families [4].

3. Genes associated with SLE

Genes associated with lupus include genes of the HLA of the MHC group of genes and non-HLA genes such as interferon genes, autophagy genes and the X-linked group genes and others. Among them, the HLA genes are those that play the most important role in the pathogenesis of lupus erythematosus. The different groups of these genes will be discussed in detail below [5].

4. HLA genes of the MHC and lupus

The human MHC genes are located in a segment of chromosome 6 (6p21.3) that consists of three areas (I, II and III) encoding three major classes of proteins: class I human leukocyte antigens, HLA divided into antigens (A, B and Cw), HLA class II (DP, DQ and DR) and class III whose components are complement, tumor necrosis factor (TNFa) and heat shock proteins. The HLA genes were the first to be associated with SLE and this since 1970. Studies in the past have identified HLA A1, B8 – a weak association in some studies with other studies showing no association at all -DR2, DR3, DQW1, DRW52, C4 null ancestral haplotypes as susceptibility genes for lupus erythematosus. HLA DR2 has been found in 75% of white patients with SLE (normal subjects 24%), 75% are positive for DR3 (normal subjects 25%), 75% are positive for DQW1 (normal subjects 55%) and 65% haveDRW52 (normal subjects 46%) [6]. Data suggest that the HLA-D region is exerting its effect on certain autoantibody responses in lupus erythematosus. Recently, the DRB1 gene polymorphisms have been associated with different sub-groups of systemic lupus erythematosus.

Different groups of SLE are defined by autoantibodies status, HLA-DRB1 polymorphisms, immunological and clinical manifestations.

Recent research has identified four different groups described below:

a. Subgroup 1 is dominated by anti-SSA/R060/Ro52/SSB autoantibodies and is strongly associated with HLA-DRB103. Discoid lesions are more common in this subgroup.

b. Subgroup 2 is dominated by anti-nucleosome/SmRNP/DNA/RNPA autoantibodies and is associated with HLA-DRB115. Nephritis is most common in this subgroup.

c. Subgroup 3 is characterized by anti-b2GPI-IgG/ANTI-cl-IgG/IgM autoantibodies and a higher frequency of HLA-DRB104 compared with other patients with SLE. Vascular events are more common in this subgroup.

d. Subgroup 4 was negative for all the above-investigated autoantibodies and was not associated with HLA-DRB1 [7].

5. HLA genes and age

Recent research has shown that HLA genes are implicated differently in the pathogenesis of lupus according to age. HLA genes are more implicated in the pathogenesis of lupus in older than in younger patients. This may be due to the fact that lupus in young patients is more related to infection while in older individuals is associated with the intake of drugs administered for various other ailments such as antihypertensive drugs, for instance, captopril [8, 9].

6. Lupus erythematosus genetics and other autoimmune diseases

An association of lupus with myasthenia gravis in a male patient has been HLA investigated and found positivity for HLA DRB1602-frequent in autoimmune disorders associated with the production of autoantibodies, DRB1401 frequent in late-onset myasthenia gravis, and A1B8 found in three of seven patients with both lupus erythematosus and myasthenia gravis [10–12].

7. Interferon genes are associated with lupus

INF—is a protein produced mainly by dendritic cells and lymphocytes following a viral infection and links innate and adaptive immunity. It confers resistance to viral infection and susceptibility to autoimmunity. Previous studies showed that interferon type I is strongly associated with the pathogenesis of lupus. The primary pathogenic factor in SLE escalates IFN-a signaling, which can activate STAT4, a transcription factor [13]. Genetic variations of this transcription factor have been associated with the risk of SLE and rheumatoid arthritis. Immature pDCs are activated through innate toll receptors TLRs, TLR7 and TLR9 by immune complexes to produce inflammatory cytokines including type I INF. High levels of serum IFN type I together with overexpression of IFN inducible genes have been found in individuals with SLE. The level of IFN correlated with the severity of the disease. The top 10 genes identified, associated with excessive production of IFN in viral infection, are I STAT1, IRF7, IRF5, IRF8 MX1, OASL, ISG15, IFIT3, IFIT1, OAS2 and GBP1 [14]. Among those, all associated with SLE only GBP1 was of recent association with the disease IRF5, IRF7 and IRF8 a family of transcription factors downstream of endosomal TLRs, are required for activating transcription of IFN-a and IFN-inducible genes [15–17]. Genetic variants on these three genes but especially variants of IRF5 and IRF7 have a functional impact on increased serum IFN and such impact depends on the presence of specific autoantibodies. The type I interferon pathway is central to disease pathogenesis. Hydroxychloroquine acts therapeutically on lupus by inhibiting the interferon pathway [18].

8. Complement genes and lupus

Evidence has revealed that complement deficiencies result in a reduced ability in the clearance of apoptotic cells that increase the production of autoantibodies and therefore SLE development in susceptible individuals. The C1q component – the first component of the classical complement pathway - that plays a significant role in the apoptotic cells is associated with SLE. C1q is encoded by three genes (a, b and c genes) all located in chromosome 1. The lupus autoantigens that are located in apoptotic debris may stimulate an inappropriate immune response. C1q may inhibit IFN-gamma production and, in this way, is involved in SLE development. When hereditary homozygous deficiency in any of the three C1q genes occurs, this leads to the development of SLE in all cases. C2, C4A and C4B genes which are part of the HLA class III genes – located at chromosome 6 – constitute components of the classical complement activation pathway. Observed in 0.01–0.02% of the general population C2 deficiency is the commonest but in lupus patients its prevalence is significantly higher depending on the region, 0.4% – 2.33% of people of European origin carry C2 deficiency – caused by a deletion on the DRW2 haplotype. These individuals will eventually develop lupus in their lifetime. C4 is important as a single gene defect. About 70% of the known cases of double homozygous C4 deficiency (C40, deficient at both C4A and C4B genes) result in a lupus phenotype. The C4A null allele is associated with almost every SLE population studied to date and may have an independent HLA effect [19].

9. Fc-gamma receptor gene polymorphisms and lupus erythematosus

The receptors for the Fc portion of IgG (FcγRs) play an important role in the clearance of immune complexes. They also present the modified antigen to the different populations of lymphocytes and are implicated in the modulation of inflammatory processes within the human immune system. Pre three families of FcγRs exist, the FcγRI, is the high-affinity receptor, while FcγRII and FcγRIII are low-affinity receptors. Failure of FcγR mediated clearance of immune complexes and control of inflammatory responses are thought to be predisposing factors for the development of SLE. The FCGR2/3 locus on chromosome 1q23.3 that encodes the low-affinity FcγRs is subject to both single nucleotide polymorphisms (SNP) and copy number variation (CNV). An SNP in the promoter region of FcγRIIb, also known as 2B.4, was found to be more frequently present in lupus [20].

10. Cytokines and SLE

IL-10 is a pivotal cytokine which inhibits T cells and antigen-presenting cells while enhancing B-cell survival and activity. IL-1β, IL-10 and TNF-a genes are important in the pathogenesis of SLE. It has been found that ILβ-511, IL-1β + 3953, IL-10-1082 and TNF-a-308 polymorphisms may be linked to the risk of lupus development and also to a specific phenotype. The high TNF alpha genotypes - 308AA - were associated with SLE independently of IL10 alleles, but the risk of developing CCLE and the prevalence of discoid lesion phenotype - in SLE - were higher in the high IL10/low TNF alpha producer group (−1082/−308GG). In addition, interaction between different cytokines modifies the appearance of autoantibodies. Patients who produce low levels of both TNF alpha and IL10 present anti-Sm-antibodies while patients who produce low IL10/high TNF alpha present more frequently antibodies to SSa and SSb.

Furthermore, interleukin 23R gene polymorphisms especially the IL23Rrs10889677 confers SLE susceptibility to individuals of certain ethnicities, such as IL17 A haplotype polymorphisms. In addition, Interleukin-1 receptor antagonist gene polymorphism is a disease severity factor in SLE [21–24].

11. Nuclear factor kappa-B (NF-κB) and lupus

NF-κB is an inflammation driving factor that mediates the release of IL-6, IL-12 and TNF. In healthy individuals, the A20 binding inhibitors of NF-κB (ABINs1–3) help keeping it in an inactive form in the cytoplasm. It is its activation followed by phosphorylation and degradation and subsequently induction of gene expression that is associated with the pathogenesis of SLE. The gene encoding the ABIN1 protein presents polymorphism that is associated with a predisposition for autoimmune disease. The TNIP1 (TNFAIP3-interacting protein 1) gene locus that encodes for the protein ABIN1 is associated with predisposition to SLE [25].

12. ITGAM gene and SLE

ITGAM produces macrophage antigen 1(MAC1), an adhesion molecule found on the surface of myeloid cells, natural killer cells and a subgroup of B cells. This is achieved when CD11b-integrin Am - encoded by ITGAM - is united to C818-integrin β2. Leucocyte adhesion and migration may be influenced by MAC1 as it binds to intercellular adhesion molecules - ICAM1 and ICAM2. In addition, MAC1 is a receptor for the cleaved complement factor IC3b. A polymorphism of this gene, particularly the R77H - a single nucleotide polymorphism -(SNP), is associated with SLE by modifying the structure of the gene products. This results in an increased production of proinflammatory cytokines and a reduced Ic3b phagocytosis and cellular adhesion. This makes this polymorphism a probable therapeutic target for lupus treatment. ITGAM gene polymorphisms result in defective clearance of immune complexes and apoptotic cells and lead to initiation and maintenance of autoimmune responses and chronic inflammation in SLE. ITGAM gene polymorphisms are associated with increased susceptibility to CCLE rather than to SLE [26].

13. PPP2CA gene and SLE

The protein phosphatase PP2A consists of three subunits but evidence reveals only the involvement of the catalytic subunit PP2Ac in the pathogenesis of SLE. PP2A controls various cellular pathways including DNA replication, gene translation and cell differentiation. The enzymatic activity of thePP2Ac is augmented in SLE. PP2Ac is dysregulated in SLE, resulting in altered transcription factor activation in T cells that affects their function by decreasing their capacity to produce IL-2 and reducing their expression of the T cell receptor (TCR) associated signaling molecule CD3ζ [27].

14. SIAE gene and SLE

Cd22 - also known as SIGLEC2 - is a lectin that belongs to the sialic acid binding immunoglobulin-like lectin family. It is expressed by B cells and functions as a negative

regulator of B cell activation. Accordingly, deficiencies of SIAE and CD22 produce phenotypes characterized by hyperactive B cells and spontaneous autoimmunity as in SLE in animal models. In fact, exon sequencing of the SIAE gene in a small group of patients with high titers of antinuclear antibodies (13 of whom had defined autoimmune diseases) found that 2 out of 19 had rare loss of function variants of SIAE. Loss of function alleles was found to be more common in patients with autoimmune diseases [27].

15. Signaling lymphocytic activation molecule SLAMF molecules

They comprise nine type I trans-membrane glycoprotein receptors that provide potent co-stimulatory signals for the TCR-CD3, complex and mediate regulatory signals between immune cells. Defective SLAMF signals result in B and T cell abnormalities and impaired antibody production. SLAMF 3 and SLAMF 6 molecules are expressed at higher levels on T cells in patients with lupus contributing to SLE pathogenesis [27].

16. PTPN22 and SLE

Protein tyrosine phosphatase non-receptor type 22 (PTPN22) is a negative regulator of T cell activation associated with several autoimmune diseases and SLE. In individuals of European ancestry, The rs2476601 is the most significantly with SLE associated polymorphism expressed at higher levels on T cells from patients with lupus contributing to SLE pathophysiology [27, 28].

17. BLK and BANK1 genes and lupus

Variants of those two genes which are present alone or in combination in a substantial proportion of lupus patients impair suppression of IRF5 and type-I IFN in human B cell lines and likely contribute to genetic risk [29].

18. PD-1 gene and lupus

PD-1 (Programmed Cell Death Protein 1) discovered in 1992 and described as the rheostat of the immune reaction, because expressed in cells of the lymphoid tissue it inhibits their effector action allowing tumour development, while its blockade induces a robust anti-tumour activity and at the same time the appearance of autoimmune phenomena. Antibodies against PD-1 are currently widely used in cancer chemotherapy but are associated with induction of autoimmunity and subsequently SLE [30].

19. Genetics of chronic cutaneous lupus erythematosus (CCLE)

CCLE in the past referred to as discoid lupus represents the papulosquamous scarring form of cutaneous lupus erythematosus. Lupus panniculitis and lupus timidus also belong to this group. Lesions similar to these of CCLE have been described in carriers of the X-linked granulomatous disease [31]. Initial research found an association of HLA-A1, B8, HLA-B15, HLA-DRB10303 and HLA-DQA1 haplotype with CCLE.

HLA-B8 was more frequently found in white CCLE patients while the HLA-DRW6 was found in an increased proportion of patients with DLE of both white and black races [32]. An association of HLA-DRB116 with CCLE in Mexican mestizo patients, the HLA-DRB116 gene is associated with most immune disorders mediated by the production of autoantibodies [33]. In a homozygous C2 deficiency patient with CCLE lupus, the C2 deficiency gene was associated with HLA-A10, B18, DR2, C4A4B2, Bfs, on one chromosome and with HLA-A2, B7 DR2, C4A4B2, Bfs on the other [34]. Susceptibility to CCLE lupus was recently noticed in a high interleukin10/low TNF alpha producer genotype (−1082 gg-308GG) [35]. A variant of the gene encoding the TRAF31P2, a member of the TNF receptor pathway involved in autoimmune diseases - missense substitution Thr438Asn - has been associated with discoid lupus and folliculitis decalvans [36]. Recently studies have identified 10 hub genes associated with CCLE which are CXCL10, CCR7, FPR3, PPARGC1A, MMP9, IRF7, IL2RG, SOCS1, ISG15 andGSTM3. Although general signs may be absent from skin in CCLE, it is a site of important disease activity. Genetic mapping recently showed overlapping of regions in seven (7) chromosomes - mainly genes of interferons and tumor necrosis factor-alpha between SLE and CCLE. In conclusion, these findings indicate that a genetic risk is shared by both SLE and CCLE [37, 38]. Micro RNA associated with epigenetic processes has also been found decreased in the serum of patients with CCLE [39].

20. Genetics of subacute cutaneous lupus erythematosus (SCLE)

Subacute cutaneous lupus erythematosus represents a widespread, photosensitive, nonscarring, nonindurated form of lupus erythematosus., associated with a distinctive immunogenetic background including the production of Ro/SS-antibodies. Patients with subacute cutaneous lupus erythematosus present in most cases the HLA-A1, B8 and DR3 haplotype that is also observed in approximately 25% of the North American Caucasians; this haplotype is now referred as the 8.1 ancestral haplotype. Partial or complete deficiency in C2 and C4, whose genes are located on chromosome 6, has been reported in some patients with SCLEA single nucleotide polymorphism (SNP) in the TNF-alpha gene promoter (−308A) encoding excessive TNF-alpha expression has been associated with skin lesions in patients suffering from SCLE (the TNF, a gene is also located within the HLA region). Also, a robust association of photosensitive systemic lupus erythematosus and a complete congenital deficiency of C1q have been recently revealed. In addition, SCLE subphenotype was significantly associated with a single nucleotide polymorphism (SNP) in the second exon of the gene encoding the A chain of C1q, which is the molecule that initiates the classical pathway of complement. SCLE patients homozygous for this SNP had lower serum levels of Ciq antigen compared to SCLE patients not having this SNP. To date this C1q an SNP is the only genetic association of SCLE that lies outside the HLA region. Two recent studies are in accordance with finding that in both SCLE and CCLE IFN-pathways are increased, but CCLE does indeed express more IFN-gamma than SCLE [40, 41].

21. Genetics of neonatal lupus

Neonatal lupus erythematosus is noticed in the newborns of women suffering from SLE, and it is characterized by an erythematosus rash around the eyes similar to spectacles, a heart block and the presence of anti-Ro antibodies in the serum.

Neonatal lupus has been associated with the HLA-DRB102, HLA-DRB103 and the-308A allele linked to higher TNF- alpha production; these are present in the majority of children with this rash [42].

22. Chilblain lupus erythematosus and the TREX1 gene

Chilblain lupus erythematosus is a rare subtype of chronic cutaneous lupus more frequently encountered in middle-aged women and can evolve into SLE in some cases. (18–20%) The clinical picture is characteristic of an acral distribution of bluish-red inflammatory skin lesions on upper and lower extremities following exposure to cold or damp weather. Rarely familial cases have been reported and are associated with autosomal dominant mutations in the TREX gene encoding the 3–5 DNA exonuclease. The TREX1 gene is located on chromosome 3p21. 0.5–3% of all patients with SLE carried mutations in TREX1 [43, 44].

23. Lupus and gender—X-linked genes associated with lupus

Lupus erythematosus is a disease that affects nine (9) times more frequently females than males. Females have a stronger immune system than males; this can be explained by evolutionary biology. Women are destined to be pregnant and during pregnancy their immune system is suppressed to tolerate the existence and development of the fetus. Therefore, their immune system has to be more robust than that of males to compensate for this relative deficiency during gestation - this is the compensation theory. According to the Lyon theory, women have two chromosomes, but one copy is turned off in every cell very early in embryonic development; this process is known as X inactivation. Recent research, however, revealed that 15 per cent of the genes of the supposedly inactivated X chromosome are still turned on that the number of certain proteins produced in women is an increase compared with that in men. Particularly in women with lupus, some genes are active on both X copies and this higher activity correlates with disease severity [45]. Anguera M has also recently discovered that in mice mature immune cells undergo significant dynamic changes that could make it easier for X-linked genes to get turned on when they should be off.

24. The AIRE gene

The AIRE gene was discovered in 1997 and plays an important role in autoimmune regulation. As it is expressed by cells in the thymus, it helps T cells to recognize if proteins presented to them are components of the self or non-self substances. It influences the expression of a wide variety of self-antigens in the thymus and is essential to the negative selection of self-reactive cells and the establishment of self-tolerance. The activity of AIRE is partially controlled by sex hormones, with estrogens and progesterone turning down the expression of AIRE while testosterone increasing its production. Under the influence of sex hormones, women at puberty make less AIRE than men, resulting in more self-reactive T cells escaping from the thymus and causing autoimmune disease. It has been discovered that the AIRE Ser196Ser synonymous variant is a risk factor for SLE.

Another X-linked gene is the gene for toll-like receptor7 or TLR-7 that encodes a protein that recognizes pathogens and increases the production of interferons - molecules directly implicated in the pathogenesis of lupus. The identification of TASL as the component that links endolysosomal TLRs to the IRF5 transcription factor via SLC15A4 provides a mechanistic explanation for the involvement of these proteins in systemic lupus erythematosus. Also, X-linked gene CXorf21 may contribute to sexual dimorphism in systemic lupus erythematosus [46, 47].

25. Epigenetic changes and SLE

Epigenetic processes are molecular events that affect gene expression by reorganizing the structure of chromatin without altering the DNA sequence [48]. Such mechanisms include:

a. CpG-DNA methylation.

b. Post-translational modification of histone tails.

c. micro RNAs (miRNAs).

Epigenetic patterns can be modified by environmental factors or internal ones such as medicines administered to the patients. SLE is one of the disorders where epigenetics plays a major role in the development of the disease. Monozygotic twins that are equipped with the same genome for SLE susceptibility present less than 50% concordance rate. This implies that other mechanisms, mostly epigenetics, are implicated in the pathogenesis of SLE.

26. CpG-DNA methylation

B and T cells from patients with SLE exhibit a global decrease in CpG-DNA methylation that correlates with disease activity. Increased methylation of the IL2 gene results in the failure of T cells in patients with SLE to express IL2, while other cytokine genes are overexpressed in T cells in patients with SLE as a result of CpG-DNA hypomethylation. Such genes include IL4, IL6, IL10, IL13, IL17 and genes encoding various surface molecules, namely CD6, CD11a, CD40L and CD70. All these events produce increased numbers of effector memory CD4+ and contribute to the proinflammatory phenotype of SLE.

27. Post-translational histone modifications

The most common histone modifications include acetylation, phosphorylation, methylation, ubiquitylation and citrullination of histone tails; however, histone modifications are even more complex than CpG-DNA methylation patterns and remain poorly understood. Histone modifications care altered in T cells from patients with SLE. These modifications result in increased TNF expression and subsequent monocyte maturation and cytokine expression. IL2 levels increase while IL17 levels augment as a result of the different expression of the relevant genes.

28. MicroRNAs

MicroRNAs are short non-coding(21–23 nucleotide) RNA molecules that act as post-transcriptional regulators of gene expression and function by forming duplexes with target mRNAs, resulting in mRNA degradation or translational arrest. MicroRNAs may be deregulated in SLE inducing the activation of type I IFN and NκB pathways and also by promoting the release of chemokines leading to exacerbation of inflammatory responses, also by reducing DNA methylation.

Molecular genetics of SLE will in the future provide the clinician with useful therapeutic tools and a cure will be achieved without even awareness of the event that initiated the inflammatory process.

Abbreviations

SLE Systemic Lupus Erythematosus.
CCLE Chronic Cutaneous Lupus Erythematosus.
SCLE Subacute Cutaneous Lupus Erythematosus.

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Chapter 6

Anti-Non-Bilayer Phospholipid Arrangement Antibodies Trigger an Autoimmune Disease Similar to Systemic Lupus Erythematosus in Mice

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Abstract

Anti-lipid antibodies are present in some infectious and autoimmune diseases, such as Systemic Lupus Erythematosus (SLE). Particularly, anti-non-bilayer phospholipid arrangement (NPA) antibodies have been detected in patients with SLE, and these antibodies trigger a disease similar to human lupus in mice. NPA are lipid associations different from the lipid bilayer of cellular membranes and, since they are transient, they are not immunogenic. However, if NPA are stabilized by drugs, they induce an immune response with the production of anti-NPA antibodies, which bind to NPA on cell membranes and generate cell lysis. As a result, intracellular antigens are exposed and trigger an immune response that generates more auto-antibodies. In this chapter, we describe the formation and stabilization of NPA, the induction of B cell responses to generate anti-NPA antibodies, and the characteristics that the disease caused by these antibodies in mice shares with human lupus.

Keywords: non-bilayer phospholipid arrangements, anti-lipid antibodies, B cells responses, autoimmunity, mouse model of lupus

1. Introduction

1.1 Cell membranes

The cell membrane is the structure that gives cells their individuality by separating them from the extracellular medium and from other cells. It regulates the transport of ions, molecules and signals towards the interior and exterior of the cell. Membranes

confer the selective permeability that maintains the differences in composition between the cytoplasm and the extracellular medium, which in turn regulates the cellular volume and the cellular response to the different signals it receives or generates. In eukaryotes, membranes divide the cell interior into compartments, or organelles [1]. Membranes are made of proteins, lipids, and carbohydrates. Proteins and lipids represent almost its entire composition, while carbohydrates represent less than 10% [2]. In particular, lipids represent from 25 to 80% of the membrane weight, and they belong to three chemical groups: phospholipids, glycolipids and sterols. All membrane lipids are amphipathic molecules that have an hydrophilic region and an hydrophobic region. Phospholipids and glycolipids spontaneously assemble into closed bilayers in aqueous mediums and constitute the membrane matrix [1, 3].

1.2 Molecular shape of membrane lipids and their molecular associations

X-ray diffraction studies of membrane lipids have shown that the area of their polar regions (A_O) significantly varies in comparison with the cross-sectional area of their hydrocarbon chains (A_H). These studies have revealed three molecular shapes: cylindrical (**Figure 1A**), conical (**Figure 1B**) and inverted conical (**Figure 1C**) [4]. In cylindrical lipids, the area of the polar region is almost equal to the cross-sectional area of the non-polar region, so the A_H/A_O ratio is close to 1. In conical lipids, the area of the polar region is less than the cross-sectional area of the non-polar and A_H/A_O is >1; while in the inverted conical lipids this relationship is inverse and A_H/A_O is <1 [5]. Cylindrical lipids, such as phosphatidylcholine (**Figure 1D**), phosphatidylglycerol, phosphatidylinositol, phosphatidylserine, and sphingomyelin, associated in aqueous medium to form closed bilayers or liposomes (**Figure 1E**), and represent 60 to 70% of membrane lipids. Conical lipids, such as phosphatidate (**Figure 1F**), phosphatidylethanolamine, diacylglycerol, and cardiolipin, assemble into an hexagonal phase II (**Figure 1G**), which consists of hexagonally packed cylinders, with the polar regions directed towards the interior of the cylinder where they form an aqueous pore of around 50 Å in diameter [5]. Inverted conical lipids, such as lysophospholipids and gangliosides (**Figure 1H**), assemble into a micellar phase (**Figure 1I**), with the polar regions towards the outside and the non-polar regions towards the inside. The membrane has lipids with the three molecular forms, and the higher proportion of cylindrical lipids compared to conical and inverted conical lipids allows the association of these three kinds of lipids into bilayers. However, membrane lipids can also have different molecular associations. ^{31}P NMR studies have indicated the presence of lipids associated in non-bilayer phospholipid arrangements (NPA) (**Figure 1J**) in membranes with high metabolic activity, such as in cancer cells and in rat liver microsomes [6].

1.3 Supramolecular organization of cell membranes

Singer and Nicolson proposed the fluid mosaic model for cell membranes in 1972. In this model, the integral proteins are inserted in the lipid bilayer, which constitutes the mosaic, and it is fluid because the interactions between lipids and between lipids and proteins are non-covalent, which allows these molecules to move laterally across the membrane.

In cell membranes, the role of lipids is mainly structural, and the type of fatty acids they contain determines the fluidity of the membrane. The hydrophobic effect

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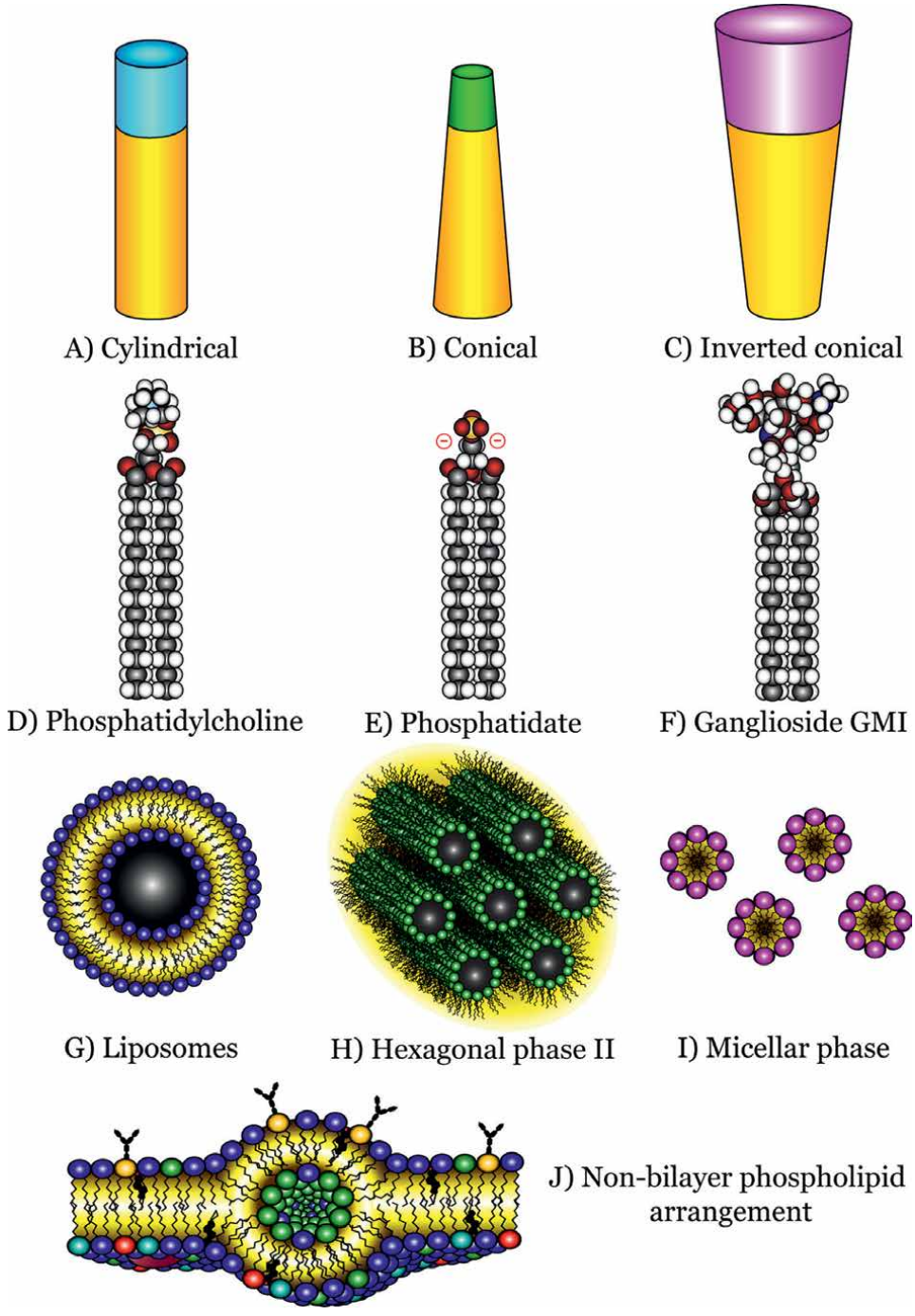

Figure 1.
Classification of membrane lipids based on their molecular shape. The lipid molecular shape (A–C) depends on its chemical structure (D–F). In addition, the three-dimensional association of lipids in an aqueous medium (G–I) depends on the lipid molecular shape. Diagram of lipids associated in a non-bilayer phospholipid arrangement (J).

is the main force that maintains the organization of proteins and lipids in this model. The thickness of cell membranes, with their peripheral and integral proteins, is around 100 Å [7, 8].

Although the fluid mosaic model explains multiple properties of cell membranes, it does not consider the cylindrical, conical and inverted conical molecular shapes of lipids, nor their functional role. Cullis and colleagues proposed the metamorphic mosaic model, where the bilayer is formed by lipids of the three molecular forms, and may temporarily have lipid associations different from the bilayer, such as NPA (**Figure 1J**). These structures, which form a microdomain, may participate in many cellular functions, including phagocytosis, membrane junctions, transport of ions and polar molecules, membrane fusion in exocytosis and endocytosis, protein insertion, and formation of polar pores and compartments [4]. The importance of this model lies in proposing lipid associations different than the lipid bilayer, like NPA, which participate dynamically in membrane functions. Therefore, they attribute a functional role to lipids, in addition to the structural role of Singer and Nicolson.

Lipids are generally poorly immunogenic molecules [9]. From the two molecular associations that can occur in cell membranes, the lipid bilayer is considered to be the least immunogenic, because it constitutes the lipid matrix of all cell membranes. NPA are also poorly immunogenic, since they are transitory and therefore are not detected by the immune system; however, if they are stabilized by amphipathic molecules, an immune response is induced with the production of antibodies against these lipid structures [10]. Among the molecules that have been found to stabilize NPA are drugs that, as a side effect, induce a disease similar to Systemic Lupus Erythematosus (SLE) in humans. SLE is a chronic, multifactorial autoimmune disease with an unknown etiology. SLE patients present anti-nuclear, anti-histone, anti-cardiolipin and anti-DNA auto-antibodies that can form antigen-antibody complexes that damage multiple organs. This disease can affect the skin, joints, blood cells, kidneys and the nervous system [11]. The most common clinical manifestations are extreme tiredness, unexplained fever, skin rash, malar rash, and arthritis. Serious complications can also occur, such as lupus nephritis and autoimmune cytopenias [12]. SLE mainly affects women in a female to male ratio of 9:1 [13]. This disease can develop at any age; however, in most cases it occurs between the ages of 24 and 32 during the fertility peak, so female sex hormones are considered a key factor in the development of this disease [14]. According to the Lupus Foundation of America, at least 5 million people worldwide have lupus. There is a higher prevalence and incidence among the Hispanic, Asian, and African-American populations [15].

1.4 Drug-induced lupus in humans

Drug-induced lupus its generated by the chronic intake of certain drugs, which induce an immune response that triggers a disease that is very similar to, but less severe than SLE. There are about 38 drugs that cause drug-induced lupus, including hydralazine, procainamide and isoniazid, which are responsible for most of the cases [16]. The exact mechanism that leads to drug-induced lupus is not well understood; however, one factor that predisposes to its development is the rate at which drugs are metabolized, which is markedly decreased in patients with a genetic deficiency of N-acetyl transferase. These patients have a higher incidence of drug-induced lupus [17].

In addition, it has been reported that these lupus-inducing drugs can suppress central and peripheral tolerance, alter gene transcription in T and B cells, alter the balance and function of cytokines or their receptors, and modify the structure of

chromatin and self-antigens [17–19]. Another possible mechanism that would explain the involvement of these drugs in the development of lupus is the stabilization of NPA on cell membranes, which then become immunogenic. We have explored this mechanism in a mouse model of lupus induced by drug-stabilized NPA on liposomes [20].

1.5 Mouse models of lupus

Mouse models of lupus have been very important to understand the genetic, cellular and molecular mechanisms of this autoimmune disease [21]. B/W mice, MRL/*lpr* mice and BXSB mice have been the most frequently used mouse models of lupus. New Zealand Black (NZB) mice develop autoimmune hemolytic anemia in the early stages of their lives, with reticulocytosis, jaundice and splenomegaly. Anti-nuclear antibodies are found in these mice, although generally in low titers [21]. The cross between NZB mice and New Zealand White (NZW) mice produces B/W mice, which develop a more aggressive autoimmune disease than that of NZB mice; this disease has similar characteristics to human lupus. B/W mice have mutations in the major histocompatibility complex (MHC) genes, and present high titers of anti-nuclear and anti-DNA antibodies, and glomerulonephritis caused by immune complexes [22]. Females B/W mice are more severely affected than males [23].

Murphy-Roths large (MRL)/*lpr* mice have a mutation on the Fas gene, which leads to deficient B and T cell apoptosis. These mice present non-malignant lymphoid proliferation and manifestations of autoimmunity, including the production of anti-DNA and anti-ribonucleoprotein antibodies, glomerulonephritis, vasculitis, and arthritis [22]. BXSB/Yaa mice have a duplicated genome section that includes the toll-like receptor 7 (*Tlr7*) and the phosphoribosyl pyrophosphate synthetase 2 (*Prps2*) genes. These mice spontaneously produce anti-DNA antibodies and develop an immune complex-mediated glomerulonephritis that resembles the glomerulonephritis of SLE patients. In contrast with B/W mice and MRL/*lpr* mice, male BXSB/Yaa mice are more severely affected by the disease than females [24].

In B/W mice, MRL/*lpr* mice and BXSB mice, a genetic abnormality alters the regulatory mechanisms of the immune system and promotes the development of autoimmunity. In other mouse models, a lupus-like disease can be induced in mice that are not genetically susceptible to autoimmune disease. This category includes mice that develop lupus after receiving DNA/protein or RNA/protein complexes [25, 26], or after receiving pristane (2,6,10,14-tetramethylpentadecane) [27, 28], and it also includes the mouse model of lupus induced by drug-stabilized NPA on liposomes.

1.5.1 Mouse model of lupus induced by lipids associated in NPA

This mouse model of lupus can be developed by the administration of liposomes bearing drug-stabilized NPA, or by the administration of the NPA-stabilizing drugs alone; these drugs include chlorpromazine (anti-psychotic), hydralazine (anti-hypertensive - diuretic) and procainamide (anti-arrhythmic) [20]. Mice develop IgG anti-NPA antibodies, followed by anti-cardiolipin, anti-histone, anti-nuclear and anti-coagulant antibodies. They present moderate alopecia, symmetrical facial lesions similar to those observed in SLE patients, and immune complex deposits between the dermis and the epidermis, in the walls of the glomerular capillaries and in the glomerular mesangium, as occurs in SLE. The symmetrical facial lesions and the deposition of immune complexes between the dermis and the epidermis are unique features of this mouse model that have not been described in other mouse models of lupus.

In this mouse model, drug-stabilized NPA become immunogenic and induce the production of anti-NPA antibodies, which are of the IgG class. Anti-lipid IgG antibodies have been detected in infectious diseases caused by mycobacteria [29] and in autoimmune diseases such as SLE [30]. For protein antigens, the development of IgG antibodies implies an isotype switch in germinal center reactions [31], but these events have practically not been studied *in vivo* for lipid antigens. Thus, this mouse model of lupus offers a unique opportunity to analyze the role of germinal centers, the extrafollicular reaction, and plasma cell development in response to lipid antigens.

2. Liposomes as model membranes to study the immunogenicity of lipids

Liposomes can be formed by the modified [10] reverse phase evaporation method [32], where the cylindrical lipid phosphatidylcholine and the conical lipid phosphatidate are used in a 2:1 molar ratio. The higher proportion of cylindrical lipids allows the liposome to form a lipid bilayer association (smooth liposome) (**Figure 2A**). When the NPA inducers chlorpromazine (**Figure 2B**), promazine, procainamide or hydralazine are added, they interact with the conical lipids and generate a lipid rearrangement that forms an inverted micelle that is the center of the NPA (**Figure 2C**); therefore, a liposome bearing NPA is formed (**Figure 2D**). These drugs are used to treat completely different disorders, but they all cause as a side effect a disease similar to SLE [17]. These drugs are amphipathic, so they have a high affinity for lipid bilayers. When the drug is inserted into the liposome bilayer, it diffuses freely until it interacts with a phosphatidate molecule. This interaction is facilitated because the drugs have a positive charge and a triangular shape, while the phosphatidate has a conical shape and two negative charges (**Figure 1B** and **E**).

2.1 Analysis of NPA formation on liposomes

The formation of NPA on liposomes can be detected by flow cytometry [33]. In this technique, the laser beam dispersion by a liposome gives information regarding the liposome size and membrane complexity. The reverse phase evaporation method described above was designed to obtain unilamellar liposomes. Therefore, the size of the smooth liposomes is very similar to the size of the liposomes bearing NPA. With the use of other techniques like the thin-film hydration method that produce multilamellar liposomes, liposomes with more heterogeneous sizes are obtained. The membranes of smooth liposomes have less complexity than the membranes of liposomes bearing NPA. This difference in membrane complexity is revealed because the laser beam dispersion is higher in liposomes bearing NPA than in smooth liposomes [20, 34].

2.2 Liposomes with drug-stabilized NPA induce a lupus-like disease in mice

The development of this mouse model of lupus is based on the generation of an immune response against NPA that leads to the formation of anti-NPA antibodies. These antibodies bind to the NPA that are naturally present in mouse cells and cause their lysis [10, 33]. This model of lupus can be induced in three ways [10, 20, 35]:

1. Direct administration of the drugs chlorpromazine, promazine, hydralazine or procainamide to mice. In this case, the drugs stabilize NPA on mouse cell membranes.

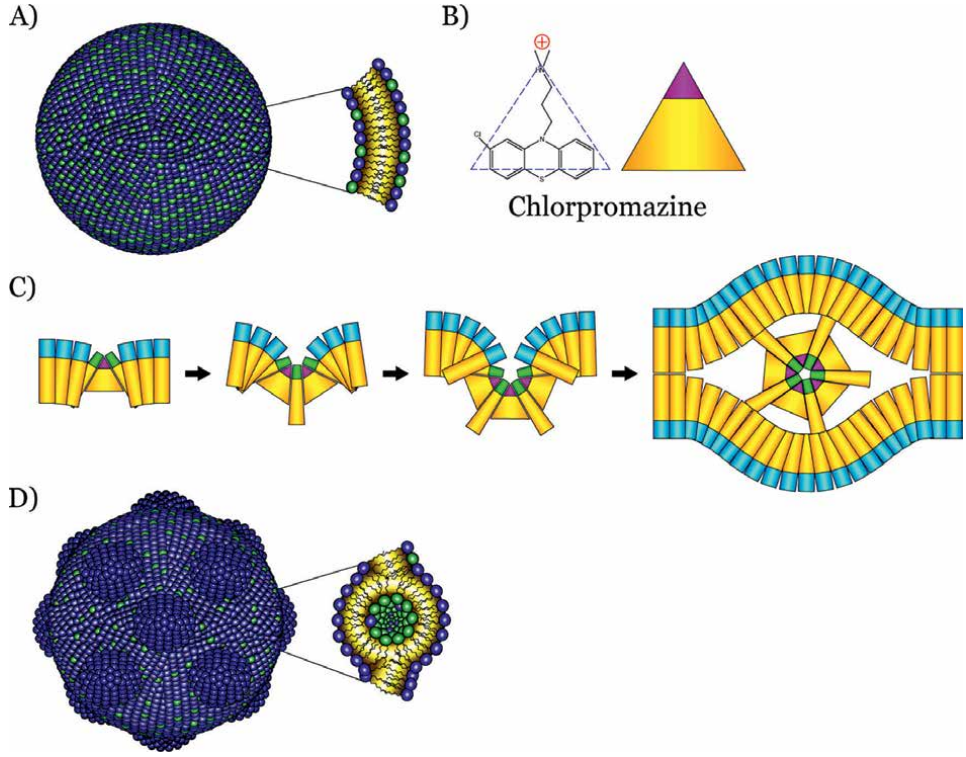

Figure 2.
Molecular structure of liposomes and NPA formation. Smooth liposomes made of phosphatidylcholine (blue polar head) and phosphatidate (green polar head) in a 2:1 molar ratio form a lipid bilayer (longitudinal view) (A). The drugs that induce NPA such as chlorpromazine, are amphipathic molecules with a triangular shape and a positive charge (B). When the NPA-inducer chlorpromazine (pink) is added to the smooth liposomes, it mainly interacts with phosphatidate, because this lipid has a conical shape with two negative charges. This interaction induces a lipid rearrangement that forms an inverted micelle that is the center of the NPA (C). In liposomes bearing NPA, most of the phosphatidate is forming inverted micelles inside NPA (longitudinal view) (D).

2. Administration of liposomes bearing drug-stabilized NPA to mice.

3. Administration of the H-308 monoclonal antibody to mice. This antibody is specific for NPA, and binds to the NPA on mouse cell membranes, causing their stabilization.

The administration of liposomes bearing drug-stabilized NPA is the method that generates the highest titers of anti-NPA antibodies, particularly when chlorpromazine is used as the NPA inducer, because these NPA are larger and their epitopes are more exposed [20, 35, 36].

During the formation of NPA, phosphatidate molecules are shifted (as a result of their interaction with an NPA-inducing drug) from a bilayer to an inverted micelle, which lodges between the two lipid monolayers and forms the center of an NPA [33, 37]. The insertion of the micelle spreads the phospholipids polar heads that surround it and exposes new epitopes to the immune system (**Figure 3A**). This open spatial arrangement of phospholipids may favor the activation of the adaptive immune system cells, thereby leading to the formation of antibodies against the phospholipids that form the lipid bulge, which is structurally different from the surface of a normal lipid bilayer, where

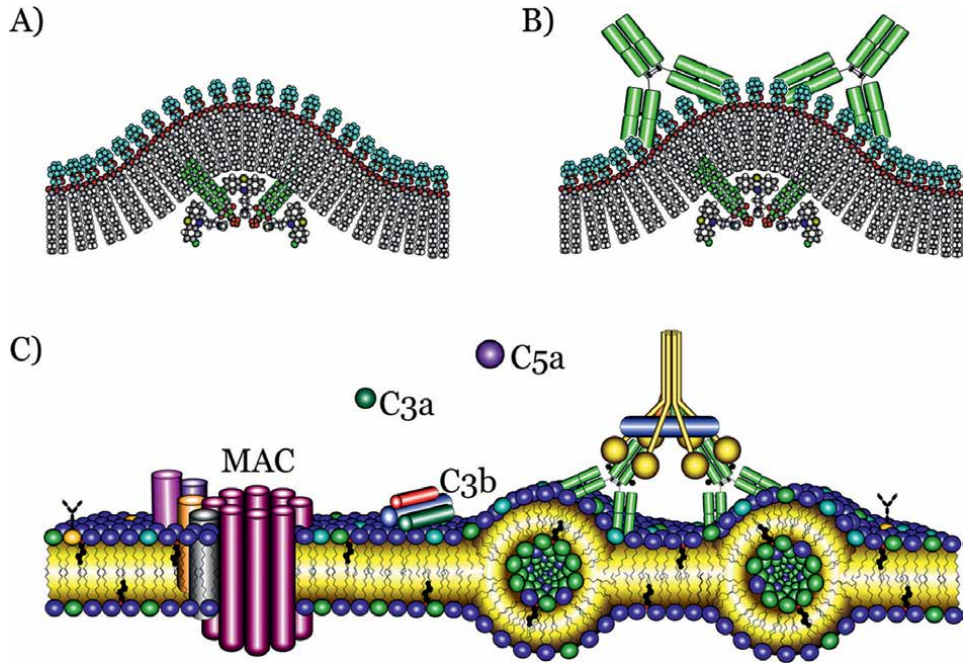

Figure 3.
Recognition of antigens by anti-NPA antibodies. Cross section of a liposome made of phosphatidylcholine (blue) and phosphatidate (green) bearing a chlorpromazine-induced NPA, which shows the spreading of the phosphatidylcholine molecules at the top of the NPA and the exposure of new antigens to the immune system (A). The immune system produces anti-NPA antibodies that recognize the polar heads of phosphatidylcholine (B). Anti-NPA antibodies bind to NPA on mouse cells and activate the complement cascade. Anaphylatoxins (C3a, C5a) are released to the medium, while opsonizing factors (C3b) bind to the cell; the membrane attack complex (MAC) is assembled and causes cell lysis.

the polar heads are not separated [1]. Anti-NPA antibodies bind to the phospholipids that are spread at the top of the NPA (**Figure 3B**), which in liposomes is the lipid phosphatidylcholine, and not to the conical phospholipids or the inducers that form the inverted micelle (this micelle is submerged between the two monolayers of phospholipids). The specificity of the anti-NPA antibodies has been demonstrated with the use of haptens that represent the polar region of phospholipids; these studies confirmed that anti-NPA antibodies recognize the polar region of phosphatidylcholine [37].

Anti-NPA antibodies are the first antibodies that can be detected by ELISA or by flow cytometry in the serum of mice that received liposomes bearing NPA [10, 20, 35]. Most of these antibodies are IgG, and their affinity increase over time [36]. Six weeks after anti-NPA antibodies are detected, anti-histone and anti-cardiolipin antibodies can be detected by ELISA in the serum of these mice [20, 36, 37]. The delayed appearance of auto-antibodies against intracellular antigens can be explained if anti-NPA antibodies cause the lysis of NPA-bearing cells (perhaps by activating the complement cascade) (**Figure 3C**) and lead to the exposure of intracellular antigens, which now become targets of the immune system.

Mice that received NPA-stabilizing drugs, liposomes bearing drug-stabilized NPA or the H-308 monoclonal antibody developed a lupus-like disease characterized by piloerection, anorexia, weight loss, moderate alopecia and symmetrical facial lesions resembling the rash described in human lupus (**Figure 4**). The alopecic skin shows atrophic epidermis, diffuse lymphocytic infiltrates, an accentuated decrease

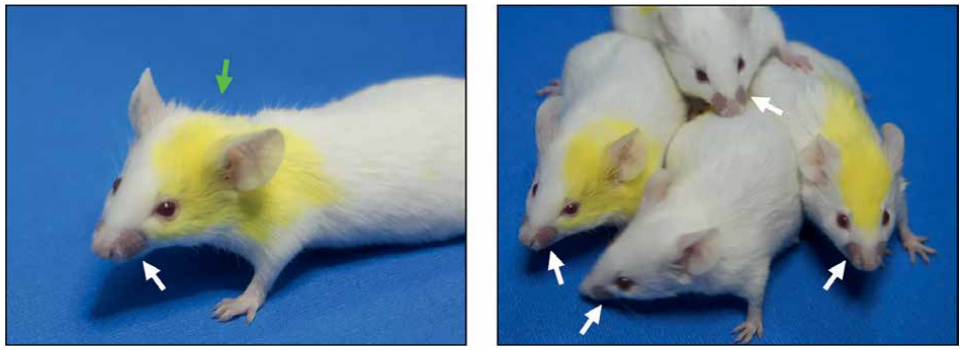

Figure 4.
Pictures of mice that develop a lupus-like disease after the administration of liposomes bearing NPA. Representative photographs of 6-month-old female BALB/c mice that received liposomes bearing chlorpromazine-stabilized NPA (mice are identified by marks made with a picric acid solution, which shows as yellow color). White arrows indicate the facial lesions. The green arrow indicates piloerection.

of terminal hair follicles, inflammation around the matrical cells of hair bulbs, and widening of the external fibrous sheath with massive disaggregation of matrical cells [10, 20]. The kidneys show a mild enlargement of the mesangial matrix with thickened capillary walls in the glomeruli [20, 37]. Immune complex deposits were also found between the dermis and the epidermis (similar to the lupus band described in SLE patients), as well as in the capillaries and the renal mesangium [10].

3. Elucidating the mechanisms that lead to the production of IgG anti-lipid antibodies

IgG anti-lipid antibodies have been detected in some infectious diseases, such as those caused by mycobacteria or in malaria, in individuals with autism-spectrum diseases and in individuals with autoimmune diseases, such as the anti-phospholipid syndrome and SLE [29, 30, 38, 39]. However, little is known about the mechanisms that lead to the production of these IgG antibodies. Understanding these mechanisms can help to understand the development of these diseases, and can lead to new therapeutic targets that improve the life quality of the patients. The mouse model of lupus induced by liposomes bearing NPA is particularly suitable to study the cellular and molecular mechanisms that lead to the production of IgG anti-lipid antibodies.

3.1 Identification of anti-NPA antibody-producing plasma cells

Plasma cells are the differentiation product of mature B cells [40]. Plasma cells can be short- or long-lived [41]. T-cell independent responses in the extrafollicular region of secondary lymphoid organs lead to the production of short-lived plasma cells, which in mice have a lifespan of less than a week. Long-lived plasma cells are generated in the germinal centers in T-cell dependent responses; after their generation, some of these cells migrate to the bone marrow and have a lifespan of months [42, 43].

Anti-NPA antibody-producing plasma cells were identified by flow cytometry as cells that contained intracellular NPA-bearing liposomes (stained with a lypophylic dye) and intracellular IgG antibodies [36]. These specific plasma cells were found in the spleen, the inguinal lymph nodes and the bone marrow of mice that produce

anti-NPA antibodies. A higher number of NPA-specific plasma cells were found in the spleen than in the lymph nodes [36], perhaps because the spleen contains additional B cell subsets (B1 and marginal zone B cells) that can also generate plasma cells [40, 44]. Interestingly, NPA-specific plasma cells were also found in the bone marrow [36]. Bone marrow plasma cells are generally considered to be long-lived, because they receive BAFF (B-cell activating factor) family cytokines, which promote their long-term survival. These cells can secrete low levels of antibodies for months or even years after the antigen is no longer present, to provide immediate protection if there is a subsequent encounter with the same antigen [42, 43].

3.2 Determination of the NPA-specific B cell reaction pathway

B cells respond *in vivo* via the germinal center pathway or via the extrafollicular reaction pathway [45, 46]. In germinal centers, isotype switching, affinity maturation and memory generation occur. These T cell-dependent processes can increase the affinity and the specificity of the antibodies, and B cells with high-affinity antibodies differentiate into plasma cells or memory B cells [31, 45]. On the other hand, the extrafollicular reaction leads to rapid production of low-affinity antibodies, which is sometimes associated with antibody class change [46, 47].

NPA-specific B cells were identified by flow cytometry as cells that bind to the NPA-bearing liposomes with their extracellular antibodies. Mice that received liposomes bearing NPA had abundant NPA-specific germinal center B cells, which increased over time, in their spleens and draining lymph nodes. In contrast, low numbers of NPA-specific extrafollicular B cells were found in the lymphoid organs of these mice. The affinity of the IgG anti-NPA antibodies produced by these mice increased over time, which further suggests that their B cells responded to NPA mainly through the germinal center pathway [36]. In order to access the germinal center pathway, B cells require T cell cooperation. However, conventional helper T cells are believed to respond only to protein antigens, so other T cell subsets may provide cooperation to the NPA-specific B cells found in this mouse model.

3.3 Analysis of the cells that provide cooperation to the NPA-specific B cells

NKT cells are a group of thymus-dependent T cells characterized by the expression of αβ TCR and several NK cell markers (NK 1.1, NKPR1 or CD161). Their development and functions are different from those of conventional CD4 and CD8 T cells. NKT cells cooperate with B cells that react with lipid antigens, and this cooperation leads to B cell activation, proliferation and differentiation into plasma cells [48, 49]. A subset of NKT cells, known as invariant NKT follicular helper ($iNKT_{FH}$) cells, could provide cooperation to B cells, since their phenotype is similar to that of helper T cells [49]. These cells express CXCR5, Bcl-6 and CD40L, secrete cytokines and chemokines (IL-4, IFN-ɣ, IL-21 and BAFF) and are localized in germinal centers in response to the glycolipid α-galactosylceramide (α-GalCer) [50, 51] $iNKT_{FH}$ cells that are induced in response to other lipid antigens express CD40L, as occurs with follicular helper T cells (T_{FH}), which are crucial for the development of germinal centers [52]. This evidence suggests that $iNKT_{FH}$ cells could provide cooperation to NPA-specific B cells, leading to their proliferation, affinity maturation and class-switching to IgG in a germinal center reaction. It remains to be determined if $iNKT_{FH}$ cells are indeed the cooperating T cell in this mouse model. Our proposed model for the generation of high-affinity IgG anti-NPA antibodies is shown in **Figure 5**.

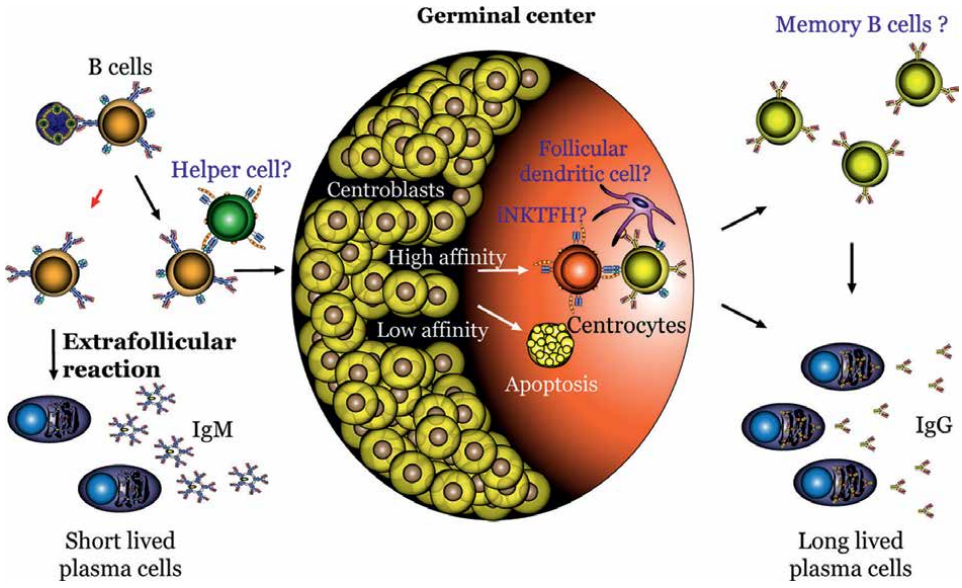

Figure 5.
Proposed mechanism for the production of anti-NPA antibodies. A naïve B cell recognizes the NPA antigen and responds. The B cell interacts with a helper T cell (possibly an iNKT cell) that induces its migration to a secondary lymphoid organ, in order to form a germinal center. In the germinal center, the B cell differentiates into a centroblast that proliferates and undergoes a series of mutations that generate low or high affinity antibodies. The centroblast then differentiates into a centrocyte, which no longer proliferates but undergoes antibody class-switching from IgM to IgG. B cells with high affinity antibodies are positively selected, while B cells with low affinity antibodies are negatively selected and die by apoptosis. When the B cell exits the germinal center, it differentiates into a memory B cell or a long-lived plasma cell that produces high affinity IgG anti-NPA antibodies. The B cells that do not receive T cell cooperation settle outside the follicles and differentiate into short-lived plasma cells that produce low-affinity IgM anti-NPA antibodies. Cell names in blue with a question mark indicate cells that have not yet been experimentally proven to participate in a germinal center specific to NPA.

4. Clinical implications of anti-NPA antibodies and future research directions

IgG anti-NPA antibodies were detected in the sera from patients that were positive for IgM or IgG anti-cardiolipin antibodies [53]. Some of these patients met four or more of the SLE criteria established by the American Rheumatism Association [54], others met the criteria for primary antiphospholipid syndrome [39], and others met the criteria for secondary antiphospholipid syndrome associated to SLE [39]. The presence of anti-NPA antibodies suggests that the NPA on the cell membranes of these patients had been stabilized; however, what led to this stabilization has not yet been identified. For example, in leprosy patients where anti-NPA antibodies have been detected, one factor that could induce the formation and stabilization of the NPA is the mycolic acid from the mycobacteria [55]. Since anti-NPA antibodies trigger a lupus-like disease in mice, it would be important to measure these antibodies in a larger number of SLE patients and in patients with other types of lupus, in order to identify if there is a relationship between the levels of these antibodies and the severity of the disease. If the anti-NPA antibodies are detected earlier than other autoantibodies (anti-cardiolipin, anti-histones, anti-coagulant) in patients with SLE, as it occurs in the mouse model, they could be used for the early detection of the disease, so that the patients could receive the appropriate treatment to prevent disease

complications [53]. It also remains to be determined if the levels of IgG anti-NPA antibodies are increased in patients with drug-induced lupus, compared to patients with non-drug related SLE, if high levels of anti-NPA antibodies correlate with a specific clinical phenotype of lupus, and if the levels of these antibodies could be used as biomarkers to monitor treatment response in these patients.

5. Conclusion

Non-bilayer phospholipid arrangements (NPA) are transient lipid associations different from the lipid bilayer. When they are stabilized by drugs, they induce the production, via germinal centers, of IgG anti-NPA antibodies; these antibodies lead to the development of a disease resembling human lupus in mice. This mouse model of lupus is suitable for the study of the molecular and cellular mechanisms that lead to the production of anti-lipid antibodies, which are currently poorly understood. In addition, this model allows us to propose that NPA and anti-NPA antibodies may contribute to the development of lupus in humans.

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Conflict of interest

The authors declare no conflict of interest.

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Section 4

Neuropsychiatric Involvement

Chapter 7

Lupus and the Nervous System: A Neuroimmunoloigcal Update on Pathogenesis and Management of Systemic Lupus Erythematosus with Focus on Neuropsychiatric SLE

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Abstract

An autoimmune condition is characterized by a misdirected immunological system that interacts with host antigens. Excess activation of T- and B-lymphocytes, autoantibody generation, immune complex deposition, and multi-organ injury are found in systemic lupus erythematosus (SLE), an early autoimmune condition with a substantial hereditary element. A number of environmental factors and lifestyle changes also play a role in the development of SLE. The imbalanced immunity could take part in the dysfunction and injury of different biological organs, including the central and peripheral nervous systems. Neuropsychiatric SLE (NPSLE) can present with focal and diffuse involvements. Clinical manifestations of NPSLE vary from mild cognitive deficits to changed mental status, psychosis, and seizure disorders. Headaches, mood, and cognitive problems are the most common neuropsychiatric presentations associated with SLE. NPSLE could be found in 40% of all people who have SLE. The diagnostic inference of NPSLE can be made solely following these secondary causes have been ruled out. The present chapter provides an updated discussion of the clinical presentation, molecular processes, diagnosis, management, and therapy of SLE with emphasizing on NPSLE.

Keywords: neuroimmunology, autoimmunity, clinical immunology, systemic lupus erythematosus, neuropsychiatric SLE, immunoinformatics

1. Introduction

Autoimmune diseases occur due to the response of the adaptive immune system to self-antigens and mediators as well as tissue damage, leading to breaking

self-tolerance. Autoimmune diseases can be divided into two groups. The first group particularly involves an organ, such as type 1 diabetes mellitus (T1DM) and thyroiditis. The second group, however, presents itself in the form of systemic complications [1]. Systemic disorders affect some organs and tissues such as the eye and optic nerve, skin, and joints. Systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and multiple sclerosis (MS) are good examples of autoimmune diseases with multiorgan involvement [2, 3].

SLE is a long-lasting, febrile, proinflammatory multiorgan disease of the connective tissue, primarily involving the skin, joints, and serosal membranes [2, 4]. Moreover, SLE is associated with various diseases including neurological conditions (stroke, seizure, cranial neuropathy, and cognitive dysfunction), serositis, leukopenia, thrombocytopenia, antiphospholipid syndrome, lymphadenopathy, autoimmune hemolytic anemia, fever, arthritis, Livedo reticularis, renal disease, Raynaud's phenomenon, oral ulcer, and malar rash [5]. The disease often affects women, Black, Hispanic, and Asian populations (ten times more frequently in women compared to men).

NPSLE or central nervous system (CNS) lupus denotes the condition where lupus influences the brain, spinal cord, and other nerves. Interestingly, SLE can affect the nervous system as neurological (N) and psychiatric (P) syndromes that are known as neuropsychiatric SLE (NPSLE) [6, 7]. NPSLE could be found in 40% of all people who have SLE. The prevalence and incidence of SLE vary based on the region, sex distribution, ethnicity, and socioeconomic factors. For example, the incidence rate of SLE in the US Medicare population varies between 3.7 and 49.0 in 100,000 person-year and the prevalence rate varies from 48 to 366.6 in 100,000 person-year. But in Europe, the incidence rate of SLE ranges from 1.5 to 7.4 per 100,000 person-year and the prevalence rate ranges from 29.3 to 210 (Global incidence rate ranges from 1.5 to 11 per 100,000 person-year and the prevalence rate varies between 13 and 7,773.5 per 100,000 person-year). It is expected that the mortality rate will decrease in the future [8]. By contrast, several essays show an increase in case numbers [9, 10].

To understand and increase information about the pathology, etiology, and treatment of this disease, animal models are used. Several articles on the pathology of NPSLE have been carried out in various aspects, such as genetic model design, complement system, cytokine involvement, and auto-antibody against brain antigens [11]. NPSLE leads to disruption and augmented the penetrability of the blood-brain barrier (BBB). Environmental factors (e.g., viruses such as Epstein-Barr virus, smoking, vitamin D level, air pollution, and medication drugs) affect the neuroimmunopathogenesis of SLE [12, 13].

Scientists have been facing many research difficulties within the field of SLE. In lupus, the inflammation happens due to the attack of the immune system against tissues and organs. Yet, the precise details of mechanisms underlying SLE are unclear. Diagnosing NPSLE is difficult because clinicians have to rule out other causes, including tumors and infections. Current treatments aim to inhibit the excessive activities of the immune system and prevent organ failure. Drugs used for patients depend on the symptoms that appear [14].

The present chapter rapidly reviews recent research into the clinical presentation, molecular mechanisms, diagnosis, management, and treatment of SLE with a focus on NPSLE. Finally, our discussion offers novel insights into the role of Immunoinformatics in future clinical research.

2. Epidemiology, definition, and classification of SLE: an overview

Systemic lupus erythematosus (SLE) is a nonhomogeneous clinical disorder that has autoimmunity roots. It can be recognized via the presence of autoantibodies produced toward nuclear antigens. According to a classic description, SLE is a multiorgan condition, and affected individuals may show symptoms in highly dissimilar formats. Classification criteria have been established, partly to try to maintain homogeneity within the SLE cases in order to facilitate research efforts. The American College of Rheumatology (ACR) disseminated these criteria that were modified in 1982 [1]. These guidelines integrate clinical presentations with irregularities found in blood exams including a detection of nuclear resistant antibodies or thrombocytopenia. Once again, these criteria were corrected in 1997 to better represent the significance of phospholipid-targeting antibodies in SLE cases [15].

SLE is an insufficiently explained syndrome. Etiology and pathogenesis are not known to date. Still, SLE is a seminal condition that has been a challenge to be resolved for immunologists, biologists, geneticists, and clinicians. The condition can be detected through various, seemingly unrelated presentations. Surprisingly, these symptoms could take place in many stochastically interconnected clusters; despite this, single gene deficits could enhance a narrower range of signs/items often observed in SLE. A lack of internal coherence exists among features (criteria) that contribute to the disease. Such features are considered in the ACR and the systemic lupus collaborating clinics (SLICC) descriptions to categorize SLE. Yet, SLE is a concept because the ACR/SLICC definitions enable scientists to describe hundreds of various SLE subtypes clinically [16].

3. Neuropsychiatric SLE (NPSLE)

3.1 Clinical presentations

3.1.1 Criteria and classification

Based on the manifestations, NPSLE can be categorized into focal and diffuse. Clinical presentations of NPSLE vary from mild impairment of cognition to altered mental status, psychosis, and seizure disorders. Headaches, cognitive deficits, and mood disorders are the most commonly found neuropsychological features in SLE. Also, epileptic disorders, cerebrovascular dysfunctions, neuropathic disease, and acute confusion conditions are the common presentations linked to NPSLE [17].

The American College of Rheumatology (ACR) introduced a consensus statement that classified 19 neuropsychiatric (NP) syndromes. These neuropsychiatric syndromes can be categorized into twelve central nervous systems (CNS) and seven peripheral nervous systems (PNS) syndromes. In addition, these were divided into diffuse neuropsychiatric diseases and focal nervous system disorders [18]. The frequency of these manifestations ranges from 0.08 to 80%. Some syndromes are more common (6.4%–80%), and the other syndromes are common (7%–20%), uncommon (0.6%–11%), or scarce (0.08%–2%). Neuropsychiatric manifestations including neuromyelitis optica spectrum disorder, chronic inflammatory demyelinating polyneuropathy, and small fiber neuropathy, are as well reported in SLE; however,

these are not considered in this categorization. This categorization is not based on any precise pathological and physiological process: yet, it helps the diagnosis of SLE in the case of nervous system influence [19, 20].

3.1.2 General NPSLE presentations

Headaches, cognitive dysfunction, and psychiatric disorders (major depressive disorder (MDD), anxiety) are the most prevalent NPSLE symptoms. Neuropsychiatric manifestations usually develop in the initial stages of SLE. Previous evidence reported that up to 40% of neuropsychological presentations are detected within the initial year of being diagnosed with SLE. NPSLE manifestations can be devastating symptoms of SLE [21]. As mentioned above, NPSLE manifestations can be classified as CNS and/or PNS manifestations.

3.1.3 Pediatric NPSLE

In children, a recent work explored the presentations, therapy, and outcome of NPSLE cases. The charts of 185 children with SLE diagnosed from 1985 to 2005 in a medical center were investigated respectively. NPSLE was characterized by the ACR NPSLE descriptions. NPSLE was found in about a third of the cases. The average age of onset was 15.2 years. A fifth showed NP presentations when initially diagnosed with SLE. The most commonly observed NP findings were epileptic disorder (84.4%), cerebral infarction (28.1%), and psychosis (21.9%). Elevated average C3/C4 quantities, a reduced proportion of anti-dsDNA antibodies increased, and an amplified proportion of raised anticardiolipin antibodies were reported in NPSLE individuals compared to non-NPSLE individuals. NPSLE is common in SLE children. It is linked to heterogeneous presentations and a significant mortality rate [22].

3.1.4 CNS manifestations of NPSLE

3.1.4.1 Depression

Depressive disorder is the most frequent mood disturbance in NPLSE. Its prevalence over the course of life could reach about two-thirds of cases, however, mania is less frequent. Lately, evidence showed that depression in SLE is linked to several factors. High-dose prednisone was found most remarkable independent element, while global disease activity was not associated. Other influential elements were a new diagnosis of SLE, cutaneous problems, longitudinal myelitis, and belonging to an ethnic group other than Asia. Therefore, in certain cases, SLE-associated depressive condition is linked to adverse effects of treatment rather than with disease activity. Based on this notion, clinicians are encouraged to reduce prednisone doses or avoid its use [23]. A link between depressive disorders and exclusive antibodies produced against at NMDA receptor, ribosomal-P, and other neural epitopes has been found. More study is required to decipher the underpinnings of SLE-related depression and further therapy.

3.1.4.2 Headache

The association between SLE and headache has been well-researched, however, the findings were inconsistent. Although some previous reports have found enhanced

headache occurrence in SLE cases, other experiments have not reported an elevation in the headache prevalence in comparison the healthy individuals.

Primary headaches, in particular tension-type headaches (TTH) and migraine, are frequent findings in NPSLE. However, secondary etiology of headache must be ruled out, such as cerebral venous sinus thrombosis, brain vasculitis, meningitis, and subarachnoid hemorrhage. The phrase 'SLE headache' is defined as a critical chronic headache for which narcotic painkillers are not effective. Lupus headache is defined as an element within the disease spectrum and therefore was classified as one of 19 neuropsychiatric diseases in ACR criteria for NPSLE [24].

3.1.4.3 Seizure

Generalized and focal seizures could occur in 10 to 20% of SLE cases. Seizures usually develop soon after the diagnosis of SLE [25].

3.1.4.4 Cerebrovascular disease

The occurrence of temporary ischemic attacks and stroke is increased among SLE patients [26]. Cerebrovascular accident in SLE is strongly related to the presence of aPL antibodies, Libman-Sacks endocarditis, accelerated atherosclerosis, and cardio-embolism due to heart valvular abnormalities [25].

3.1.4.5 Demyelinating syndromes

Clinical findings of demyelination were reported in 0.3% of SLE cases. SLE-related-demyelination is not yet clearly understood. Therefore, notable investigation toward its diagnosis and management is required. These syndromes may include clinically isolated syndrome (CIS), could be similar to other CNS demyelinating syndromes (for instance, multiple sclerosis (MS)), result from medication, and, in certain conditions, the diagnosis could be made solely by long-term follow-up [27].

3.1.4.6 Transverse myelitis

Transverse myelitis is estimated to affect 1.5% of cases in SLE. Lately, researchers have linked transverse myelitis-SLE to aPL antibodies [28], thereby highlighting spinal cord degeneration as a result of thrombosis as an underlying mechanism. In certain situations, a similarity between Devic's disease with the existence of anti-NMO immunoglobulins is presumed. In the rest of the situations, transverse myelitis could turn into MS [25].

3.1.4.7 Movement disorders

Chorea is the most frequent movement problem in SLE and develops in 2 to 3% of SLE cases and this percentage is more in children, while ataxia, Parkinsonism, and hemiballismus are somewhat scarce symptoms in SLE patients. Chorea often occurs during the first years of SLE diagnosis and is found by aPL antibodies in up to 92% of patients [29, 30]. It has been proposed that such antibodies pass through the BBB, attach to nerve cells' antigens, and ultimately lead up to this symptom [31].

3.1.4.8 Aseptic meningitis

Aseptic meningitis can be a neurological finding of ongoing SLE. Other etiology of aseptic meningitis, including pharmacotherapy, cancer, and infections are to be excluded [25].

3.1.4.9 Cognitive dysfunction

Cognitive deficit is extremely common in lupus cases, varying within the range of 20–80% [32, 33]. It may, however, not be reasonable to attribute deficit in cognition to the activity of the disorder, SLE burden, and corticosteroid treatment [32].

3.1.4.10 Psychosis

Organic psychosis may influence 2 to 11 percent of SLE cases. In about 60% of such cases, it emerges as the SLE-symptom [34]. SLE psychosis is often associated with SLE activity and is affected by immunosuppressive treatments. One important differential diagnosis is corticosteroid-activated psychosis. However, it is not more prevalent in SLE in comparison with the rest of autoimmune conditions [35]. Studies have also detected a positive linkage between SLE and the danger of being affected by schizophrenia [36, 37].

3.1.4.11 Acute confusional state

An acute confusion condition is a diffuse CNS disease that presents as a changing grade of consciousness and loss of orientation and is equal to the concept of delirium as defined within the DSM-IV [38]. Because of a lack of a precise definition, its frequency is hard to calculate, varying within the range of 0-7% [39].

3.1.5 PNS manifestations

Peripheral nervous system (PNS) presentations influence about 10 to 15% of NPSLE patients, and multiple concepts are taken into account in the late 1990s ACR-NPSLE patient descriptions. The greater part of patients present with peripheral neuropathy [40], which comprises mono-neuropathy, poly-neuropathy, cranial-neuropathy, hyperinflammatory demyelinating poly-radiculoneuropathy, and plexopathy. A report noted that 17% of SLE-associated peripheral neuropathies are small-fiber neuropathy [41]. Small-fiber neuropathies are able to cause severe burning pain by targeting non-myelinated C fibers and finely myelinated A fibers. The diagnosis is verified via obtaining a cutaneous sample that exhibits injury to the dorsal root ganglia along with distal axons. The rest of the PNS presentations comprise autonomic disorders and myasthenia gravis [25].

3.2 Molecular mechanisms

3.2.1 Cellular and molecular processes in neuropsychiatric systemic lupus erythematosus (NPSLE)

Overactive adaptive immune cells, autoantibody generation, immunological complex accumulation, and multisystem damage are features common in SLE, an

early autoimmune disorder with a strong hereditary component. As previously stated, different elements could play a role in the development of SLE. Mutations in immunity-related genes, such as C1q, C1r, C1s, C2, or C4, which are essential elements of the complement cascade, are one of these reasons. These supplements play a role in the detection and opsonization of apoptotic cells, as well as the clearance of critical immune complexes, and their absence can result in the creation of autoantigens, as well as the stimulation of interferon (IFN) types 1 and 2 [42, 43].

Other mutations in genes that regulate nucleic acid metabolism, including TREX1, RNASEH2B (A, C), ADAR, IFIH1, and SAMHD1, trigger SLE-like symptoms that are mediated by a type I chronic response to IFN. Alleles associated with the B cell response (BLK, BANK1, FCGR2A, and PTPN22) as well as alleles associated with the innate immunological response (IRF5, STAT4, TNFAIP3, and TNFSF4) are also associated with SLE [44, 45].

In SLE, epigenetic modifications include DNA methylation, histone modifications, and noncoding transcripts. DNA methylation suppressors can induce T cell reactivity and lupus symptoms in mice and humans. In addition, T cells from patients with SLE have less methylation than T cells from healthy individuals. Studies of single-site methylation reveal that SLE patients had unique mutations in the PRF1, TNFSF7 (CD70), ITGAL, and CD40LG genes, among others [46, 47]. SLE pathogenesis is associated with aberrant histone acetylation, which is associated with higher histone H3 and H4 acetylation in human CD4 SLE T cells [48]. In SLE patients, the expression of miR-126-3p, miR-let7d-5p, miR-15a-5p, miR-326, miR98-5p, miR143-3p, miR-7, miR 21, and miR22 increased, whereas miR-31 and miR-146a, the negative regulator of IFN type I signaling, decreased. Negative regulators of IFN type I signaling, miR-31 and miR-146a, were decreased in SLE patients. In SLE B cells, miR-7, miR-21, and miR-22 levels were all elevated relative to the control group, and all three miRs suppressed PTEN expression. Reduced PTEN expression in SLE B cells correlates with B cell hyperactivity and the potential failure of B cell tolerance, suggesting that this microRNA may play a role in the etiology of SLE. Let 7 levels were seen to fluctuate in lupus nephritis samples, suggesting that it suppresses NFkB signaling. SLE patients and lupus nephritis tissue samples exhibit increased NFkB signaling in B cells. Reduced miR-31 expression is associated with lower IL-2 expression in SLE patients, indicating that miR-31 plays a mechanical role in the disease [49–51].

3.2.2 NR2A/B antibodies of anti-N-methyl-d-aspartate (NMDA) receptor subunit

Neurons contain the glutamate receptor and ion channel NMDA. 30–40% of SLE patients' sera include antibodies against the NR2A/B subunit of the NMDA receptor. After establishing evidence of R4A antibody (as anti-dsDNA antibody) interaction with NRDA NR2A and NR2B receptor subunits, researchers sought similar antigenic characteristics in polyclonal anti-dsDNA antibodies in SLE patients. Anti-NR2A/B antibodies induce apoptotic cell death in cell culture, according to prior investigations. Anti-NR2A/B antibodies were injected into the hippocampus of C57BL/6 mice, causing neuronal death. In addition, intravenous administration of anti-NR2A/B antibodies to BALB/c mice treated with LPS resulted in antibody binding to hippocampal neurons and nerve damage [52, 53].

3.2.3 Matrix metalloproteinases (MMPs)

MMPs are a class of zinc- and calcium-dependent endoproteinases involved in the degradation and regeneration of extracellular matrix proteins. MMPs, especially

MMP-9, are able to degrade basal layer components such as collagen type IV, fibronectin, and laminin, as well as aid in proteolyzing the basal layer, resulting in BBB disruption. Numerous immune-type cells (granulocytes, lymphocytes, and monocytes) release MMP-9, with neutrophils being one of the most prolific sources. Serum and CSF levels of MMP-9 in SLE patients with CNS involvement are elevated, according to the available evidence. MMP-9 levels in the CSF are also associated with tau protein and glial fibrillar acid, markers of neurodegeneration and astrocytic degeneration, respectively, in SLE patients [54, 55].

3.2.4 Neutrophil extracellular traps (NETs)

Neutrophils are guardians of the innate immune system that migrate from the bloodstream to infection sites to combat pathogens by phagocytosis, degranulation, and the release of neutrophil extracellular traps (NETs). Neutrophil extracellular vesicles (NETs), which are produced by active neutrophils, are a distinct kind of cell death from necrosis and apoptosis. NETs with fibrous structures contain histones (H1, H2A, H2B, H3, and H4) and granule-derived enzymes, including neutrophil elastase, myeloperoxidase, and MMP-9. Antibacterial characteristics exist within histones. In addition to elevated reactive oxygen species (ROS) in neutrophils, transmission across activated endothelium in vivo stabilizes NET formation and may result in cell death. Neutrophils in SLE patients have altered functional characteristics due to the overexpression of granulopoiesis-related genes, such as decreased phagocytic capabilities, increased intravascular activation, increased platelet-neutrophil accumulation, and increased production of reactive oxygen species [56, 57].

3.2.5 Pro-inflammatory mediators

In the hippocampus of animal models with NPSLE, infiltration of CD3+ T cells and enhanced mRNA expression of proinflammatory mediators including IL-1, IL-6, IL-10, interferon (IFN)- and transforming growth factor were observed. In the CNS, cytokines are produced by neurons and microglia. Studies have indicated that neurons and microglial cells are capable of synthesizing IL-2, IL-6, IL-8, and IL10 intrathecally. Levels of IL-6 in the cerebrospinal fluid (CSF) were associated with abnormal brain MRI signals in human NPSLE, which were predominantly white matter intensities weighted with T2. In 119 SLE patients, IL-6 CSF levels were related to MMP-9 CSF levels, suggesting that BBB failure may be involved in the development of brain MRI abnormalities in patients with NPSLE [58, 59].

3.3 Diagnosis

NPSLE is challenging to treat in clinical practice due to the variety of clinical presentations, the shortage of pathology specimens to diagnose the underlying etiology, and the paucity of evidence-based therapies [60]. Before making a definitive diagnosis of NPSLE, professionals must rule out other probable causes, such as infections and cancers, due to the disease's difficulty to identify [32, 61]. Neuropsychiatric manifestations of SLE comprise a broad spectrum of symptoms that impair patient prognosis and quality of life. Recent advances have been achieved in both improving the diagnosis of NPSLE and elucidating its etiology. For the diagnosis of NPSLE, there is no gold standard [62]. In all patients with unexplained neuropsychiatric symptoms or presentations indicative of neuropsychiatric (NP) disease, the first step

would be to investigate and characterize the NP symptoms while ruling out other common causes, such as infections, metabolic disorders, or drug use. Thrombotic events, atherosclerotic disease, cardiovascular risk factors, and general SLE activity are evaluated in greater detail [61]. Different clinical, serological, immunological, electrophysiological, and neuroimaging tests are utilized to diagnose NPSLE. Various imaging modalities and the presence of autoantibodies can aid in diagnosing the cause and the optimal treatment protocol [63]. Neuroimaging can be used to differentiate SLE patients from healthy controls, but further research is required to differentiate among lupus patients with and without neuropsychiatric symptoms. As potential markers for a more objective and accurate diagnosis, higher levels of certain substances in the cerebrospinal fluid and serum, as well as the presence of particular autoantibodies, have been detected [20, 64].

To accurately classify NP, imitators must be excluded with care. However, NP episodes must be associated with SLE in order to receive immunosuppressive therapy. To improve clinical care and research outcomes, a number of attribution models have been developed [65, 66]. Numerous practitioners now employ the well-established language of the American College of Rheumatology (ACR) to define NPSLE episodes in clinical practice [18]. Most commonly utilized are the ACR criteria from 1999, which have been validated in an external cohort with a sensitivity and specificity of 45% [67]. The ACR criteria must be amended and updated, including the addition of new manifestations, notwithstanding the considerable progress made since their release (e.g., posterior reversible encephalopathy syndrome, small fiber neuropathy, and chronic inflammatory progressive demyelination). Various classification criteria have been developed over time [18, 68–71]. Another criterion devised an attribution method that produces a probability value between 0 and 10. This algorithm evaluates four subjects during model construction, three of which are identical to those used in ACR standards. In this context, issues discussed include the existence of mild or common neuropsychiatric episodes as well as EULAR-suggested SLE risk factors [72]. As the ACR criteria displayed a high sensitivity (91%) but a low specificity (46%), Zhang et al. presented their own criteria based on five symptoms (disease activity, antibodies, thrombosis, skin lesions, and manifestations) whose positive and negative prognostic values were greater than 70% [17].

SLE patients could be evaluated for cognitive impairment, anxiety, and depression using a number of screening procedures established for neurodegenerative illnesses. ACR's ad hoc interdisciplinary committee recommended specific neuropsychological tests (NPTs) for identifying cognitive dysfunction (CD) in SLE [18]. Even for limited inspections, NPTs are time-consuming, costly, and inaccessible in a variety of situations. The Automated Neuropsychologic Assessment Metrics (ANAM), a computerized method, measures many of the same cognitive categories as the Neuropsychological Tests (NPTs) [73]. NPT and ANAM are time-consuming, somewhat costly, and difficult to obtain; hence, a simple and sensitive screening test is necessary for clinical therapy [74]. According to preliminary studies, the Montreal Cognitive Assessment Questionnaire (MoCA) is a brief and affordable screening tool that may be useful for the early detection of CD in SLE [75, 76]. In comparison to normal individuals or patients with rheumatoid arthritis, the MoCA demonstrated moderate sensitivity and specificity for cognitive impairments (0.83–0.94 and 0.27–0.46, respectively) [77]. Other cognitive decline screening instruments, such as the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), have been utilized in the elderly. The IQCODE is a questionnaire that is completed by the patient's family or an appropriate informant who knows the patient well and can

determine if the patient's cognitive function has decreased in relation to regular daily activities over time. The IQCODE is not affected by the patient's educational level, premorbid IQ, or proficiency in the culture's predominant language, but it can be influenced by the quality of the informant-patient relationship [78].

Self-informed surveys, for example, the hospital anxiety and depression scale (HADS), the Center for Epidemiologic Studies-Depression Scale (CES-D), and beck anxiety inventory (BAI) are low-cost and widely used screening utilities for depression and anxiety in the general inhabitants; however, only a handful of researches have inspected their function in SLE patients [79, 80]. Previously reported in a cross-sectional study of 159 consecutive consenting SLE adults to determine the reliability of assessment in these questionnaires' test-retest, prevalence of depression and anxiety in SLE patients, and study their diagnostic correctness (HADS-A), the prevalence of anxiety ranged from 45% (BAI) to 50% (CES-D) (CES-D) and the prevalence of depression ranged from 29% (HADS-D) to 52% (CES-D). According to the authors' conclusion, both surveys have the potential to serve as NPSLE screening tools [74].

None of the laboratory or neuroimaging biomarkers for diagnosing NPSLE have been proven accurate or reliable in clinical practice, despite extensive clinical research. Novel biomarkers may permit a more objective evaluation [81]. It might be as easy as measuring the concentration of a certain biomarker in the blood. Autoantibodies, the defining characteristic of lupus, may be useful as biomarkers. Numerous autoantibodies have been linked to NPSLE, but their role in pathogenesis remains unproven [82]. One of the potential biomarkers is 2-glycoprotein 1 and cardiolipin, which have been associated with focal neuropsychiatric diseases including cerebrovascular disease, seizures, and chorea, as well as diffuse neuropsychiatric disorders like cognitive impairment, psychosis, sadness, and headache [83, 84]. Ribosomal P protein, which is associated with NPSLE by demonstrating greater titers during active SLE in serum and CSF, is not a helpful biomarker for discriminating between disease subtypes [85–87]. Antibodies against NR2, a subunit of the N-methyl D-aspartate receptor (NMDAR), are associated with spatial memory impairment in both mice and lupus patients. NR2 is essential for synaptic plasticity and memory in the brain [81, 88–93]. Using primary brain micro-vessel endothelial cells, it was demonstrated that anti-NR2 antibodies can breach the BBB and enter the brain [94]. Several additional biomarkers, such as Microtubule-associated protein 2, were indicated to have a connection with NPSLE that was either significant or contentious (MAP-2) [95], U1 ribonucleoprotein (U1RNP) [96], and Glial fibrillary acidic protein (GFAP) [88, 97]. Although autoantibodies have been suggested as a potential biomarker, only a few antibodies, such as antineuronal, anti-ribosomal P, and anti-NR2 antibodies, have met the exploratory criteria and are being utilized in diagnosis and therapeutic decisions [98, 99].

In addition, numerous neuroimaging techniques, such as nuclear medicine techniques and magnetic resonance imaging (MRI), have enabled the assessment of functional and structural irregularities in SLE patients, thereby facilitating a greater comprehension of the underlying pathophysiology and subsequent pathophysiological alterations [6]. Since the 1980s, aberrant brain MRI has been described in SLE and NP-SLE [100, 101]. On conventional MRI (cMRI), a significant proportion of patients with NP-SLE show no abnormalities, and global markers such as lesion load or brain atrophy do not correlate with symptom severity [102, 103]. Innovative MRI techniques and software may be more precise in identifying brain variations in NPSLE patients. Researchers were able to map the microstructure of the brain utilizing mean diffusivity and fractional anisotropy (DTI), sophisticated MRI methods including

white matter hypersensitivity volumetry, diffusion-tensor imaging (DTI), and voxel-based morphometry (VBM) [104]. However, there is yet a radiological and clinical contradiction. To eliminate this uncertainty, a broad strategy and imaging surveys are required.

3.4 Management and treatment

The management of NPSLE could be challenging at multiple phases, including problems in classifying them as SLE, diagnosis based on ambiguous symptoms, and the limited and imprecise arsenal of available therapies. Initially, a thorough evaluation should be conducted to rule out alternative reasons, such as metabolic diseases, infection, cancer, and severe drug reactions. Once the symptoms are mostly attributed to SLE and these confounding variables have been ruled out, the management goals are increased. First, symptomatic medication should be administered, including antiepileptics for seizures, treatment of hypertension and metabolic abnormalities, and mood stabilizers, anxiolytics, antidepressants, or antipsychotics, as indicated, for psychiatric symptoms. Until then, therapy of the underlying SLE process should be administered in accordance with whether the neuropsychiatric manifestations are attributable to a widespread, inflammation-driven condition or a process [61]. Before further actions, it is necessary to consider the challenges associated with NPSLE management.

First, concerns unrelated to SLE should be addressed appropriately with non-SLE-related therapies. A study described the beneficial effects of psychotherapy on reducing sadness and anxiety and boosting life satisfaction [105]. Anxiolytics and antidepressants are also used to improve cognitive skills in SLE patients with anxiety and depression; however, their use in mood disorders is inconsistent [106]. Effective antiepileptics and antipsychotics are used to treat SLE psychosis and seizures, respectively [107, 108]. The cognitive dysfunction caused by SLE is managed to utilize a technique known as meta-context behavioral rehabilitation. A nonrandomized study of rehabilitation strategies revealed a 100 percent retention rate with memory self-efficacy and an improvement in quality of life [109]. This emphasizes the relevance of non-SLE concerns in the quality of life of patients. In addition, non-SLE therapies offer the potential for ameliorating these problems. To unravel the pharmacological components of this strategy, a controlled trial should be conducted.

In the absence of controlled clinical trials, certain NPSLE therapies are experimental. Depending on the underlying pathophysiology, pharmaceutical therapy in the clinical environment is aimed at reducing inflammation or preventing thrombotic events [110]. In patients with immune-mediated damage or global lupus, immunosuppressants such as corticosteroids must be provided alone, or in combination with additional immunosuppressive medications such as azathioprine, mycophenolate mofetil, and cyclophosphamide. Immunotherapy's primary objective is to treat or relieve symptoms [61]. Only oral prednisolone and intravenous cyclophosphamide have demonstrated efficacy in the treatment of NPSLE [111]. Seizures are less likely to occur in people receiving antimalarials [108]. Other co-administered medications include statins for patients with arterial or recurrent venous thromboembolism, as well as nonsteroidal anti-inflammatory medicines (NSAID) for pain management [112]. Nonetheless, the use of NSAIDs in SLE is associated with an increased likelihood of recurrent aseptic meningitis. Anticoagulants and antiplatelet treatments are used to treat ischemic NPSLE, especially in patients with positive antiphospholipid (aPL) antibodies. Typically, inflammatory and ischemic NPSLE coexist; we advise a combination of antiplatelet treatment, anticoagulation, and immunosuppressive

drugs [20]. All thromboses caused by aPL-antibody require lifelong anticoagulation with warfarin as the primary treatment [113]. Since the safety profile of antimalarials and statins is promising, they should be evaluated as alternatives to warfarin, particularly in patients with persistent thrombosis. In addition, low-dose aspirin is recommended for people with cardiovascular risk factors. Although randomized clinical trials are now underway, the available data are insufficient to recommend direct oral anticoagulants (as well as novel oral anticoagulants) to prevent aPL-antibody-mediated thromboembolic events. It is recommended to administer intravenous immunoglobulin infusions, pulse corticosteroids, and/or plasmapheresis to patients with NPSLE and severe anti-phospholipid syndrome (APS). Numerous small series and case reports found that the use of eculizumab into these treatments was beneficial [114]. There is a vast variety of pharmacotherapies for NPSLE, each of which requires careful evaluation, illustrating the sensitivity of treatment selection for this disease.

In addition, six months of oral cyclophosphamide therapy followed by azathioprine maintenance medication was successful in treating lupus psychosis. The addition of Rituximab (or a different anti-CD20 monoclonal antibody) to the NPSLE therapy procedure requires consideration, notwithstanding the unreliability of the data supporting this practice. The efficacy of Rituximab was evaluated in ten patients with persistent NPSLE who saw rapid and considerable improvement in clinical symptoms and signs, consistent with radiological findings [115]. In a retrospective study of pediatric patients with NPSLE, Rituximab was also effective and largely safe [116]. These results demonstrate that the CD20 receptor plays a critical role in the pathogenesis of NPSLE, consistent with the immune cells that express this receptor, highlighting the importance of immune system-induced inflammation in this disease.

4. Remarks for future clinical research: the role of bioinformatics and immunoinformatics

Immunological investigations are defined with the help of the generation of rapidly piling quantities of information, that is backed via genetics and proteomics projects and large-scale evaluation of pathogen- and antigen and host reactions. The need to store, handle and evaluate this quickly expanding source of biological, clinical as well as epidemiological information led to the conception of the field known as computational immunology or Immunoinformatics. Immunoinformatics employs computerized approaches or sources that can be utilized in the exploring of immune system actions. This field resides at the crossroad of experimental and computer sciences and utilizes domain-exclusive databanks, computer simulations, and approaches drawn from artificial intelligence. For instance, computational or artificial intelligence simulations are rapidly being utilized in order to trigger as well as enhance scientists' comprehension of immunity patterns, including antigen modification and antigen-presenting, and for assessment of host and pathogenic genomes [117].

Immunoinformatics has been utilized to shift the immune profile by designing immunogenic candidates which implement various epitopes that play a role in disease. We suggest that a pipeline should be developed to identify differentially expressed genes and biomarkers by Bioinformatics [118, 119] and shift the immune system via Immunoinformatics/in silico efforts (e.g., reverse vaccinology) [120–122]. Moreover, Bioinformatics can help to recognize plausible therapeutic targets by the detection of differentially expressed genes [123].

There is no definitive treatment for COVID-19 and vaccines, despite bringing major success, have failed to completely eradicate the disease and have side effects [124, 125].

In addition, guideline makers should take into account the influence of the current Coronavirus disease-2019 (COVID-19) pandemic on SLE and its CNS involvements, which are well-known [126]. A study showed that COVID-19 morbidity could be moderately raised in most SLE cases, even though restricted data can be inferred on more critical patients [127].

Cytokines and hyperinflammatory responses are common features of COVID-19 and SLE [128, 129]. Inflammasomes are valuable therapeutic targets that are implicated in a wide range of disorders, such as neuropsychiatric and neurodegenerative diseases [130], eye disorders [131], cardiovascular disorders, and others [132]. Inflammasomes have also been shown to be involved in SLE. Induction of the inflammasome, a multimeric complex that triggers caspase-1. After that, the cytokines IL-1β and IL-18 mature, which are key to SLE pathogenesis [133].

Finally, we suggest that novel antibodies other than classical factors included in SLE criteria are developed. For instance, autoantibodies to the δ-Opioid Receptor act as opioid inducers and exhibit immunomodulatory function. Anti-DOR autoantibodies may function to stimulate the cell-mediated/Th1 arm. In SLE patients, therefore, elevated levels of anti-MOR Abs could worsen the disease, whereas increasing the anti-DOR autoantibodies could aid to deviate to Th1-type immune feedback [134, 135].

5. Conclusions

Research efforts have characterized NPSLE and SLE. The significance of NPSLE, in particular, has been underrated as it affects a great portion of SLE cases. More studies should aim the development of novel treatments because, despite clinical experiment, none of the laboratory or neuroimaging biomarkers for diagnosing NPSLE have been found accurate or reliable in clinical practice. New biomarkers may enable clinicians to make a more objective assessment of patients' conditions. NPSLE therapy and management may be complicated at different phases. These difficulties are assigning patients to SLE, diagnosis based on vague presentations, and the restrictions and imprecise currently available therapy armamentarium. Development of treatments for SLE could be facilitated via Immunoinformatics/*in silico* technology to engineer and evaluate candidates rapidly. Finally, we believe the next-generation combinational therapeutic regimen should be tested to enable major advancements.

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Conflict of interest

The authors declare no conflict of interest.

Notes/thanks/other declarations

None.

Appendix A

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Chapter 8

Literature Review on Neuropsychiatric Lupus

Gerald B. Natanauan

Abstract

Neuropsychiatric systemic lupus erythematosus (NPSLE) had been described in several medical literatures These included the pathogenesis, mechanisms and current approach to management and treatment. Although still limited, more information is coming with the advancement of medical knowledge and technology regarding systemic lupus erythematosus and neuropsychiatric involvement. NPSLE remains elusive in the context of outright diagnosis and management. Its manifestations need to be carefully assessed before a final diagnosis is made for the proper treatment. Thus, attribution models were later developed to address these problems. NPSLE will likely develop among lupus patients in the first 5 years from SLE onset. The development and exact pathogenetic mechanisms of the disease also remain controversial but the discovery of the blood-brain barrier injury has given points of clarity. The focus of management is based on the identified etiology. Targets include symptomatic treatment and addressing the underlying SLE process. Likewise, the use of corticosteroids, cyclophosphamide, mycophenolate mofetil, azathioprine, antimalarial agents, warfarin or low dose aspirin depending on the pathways involved is also being utilized with positive results. More researches are being done to better elucidate the complex nature of NPSLE.

Keywords: systemic lupus erythematosus, neuropsychiatric lupus, NPSLE, autoantibody, autoimmunity

1. Introduction

Systemic lupus erythematosus is a complex autoimmune disease that affects virtually all organ systems. The interplay of the cellular make-up of the affected host and environment creates aberrancy that leads to a cascade of inflammatory response causing organ damage. The central and peripheral nervous system similar to other organs impaired by lupus exhibit more complicated manifestations. This in turn has resulted to a difficult timely recognition of the disease for an appropriate management. Within the past 10 years or more, researches worldwide are being done to address this problem. Neuropsychiatric systemic lupus erythematosus (NPSLE) had been described in several medical literatures These included the pathogenesis, mechanisms and current approach to management and treatment. Although still limited, more information is coming with the advancement of medical knowledge and technology regarding systemic lupus erythematosus and neuropsychiatric involvement.

2. Pathogenesis

The pathogenesis of NPSLE is being discussed in several literatures. There is no doubt that multiple pathogenic mechanisms are involved. Likewise, it encompasses a variety of process including cytokines, autoantibodies, and other infiltrating cells (cell-mediated inflammation).

The underlying mechanisms of neurologic manifestations depend on whether the central nervous system (CNS) or the peripheral nervous system (PNS) is being involved. For the CNS manifestations to occur, the primary injury can either be directed towards the vasculature or the brain parenchyma. The vascular injury includes damage to both large and small vessels via thromboembolic events, often as a consequence of antiphospholipid (aPL); a bland vasculopathy of small vessels characterized by vascular hyalinization, perivascular inflammation, and endothelial proliferation; and atherosclerotic lesions [1].

The disruption of BBB is central to the pathophysiology of NPSLE. This serves as the primary factor for the transit of pathogenic proteins towards the CNS. On the other hand, the BBB permeability remains debatable in diffuse NPSLE. Diamond et al. have provided data on studies from murine models supporting the role of circulating anti-DNA autoantibodies in the development of NPSLE thru cross-reactivity with the NR2 subunits of the anti-N-methyl-D-aspartate receptors during inflammation causing damage in the integrity of BBB [2, 3]. Other substances which are also associated with NPSLE include intrathecal IgG production, antiphospholipid (aPL) antibodies, anti-ribosomal P antibodies, anti-endothelial cell antibodies (AECAs), anti-microtubule-associated protein 2 (MAP-2) antibodies, anti-aquaporin 4 antibodies (AQP4) and anti-suprabasin antibodies (**Table 1**). Meanwhile, intrathecal markers associated with NPSLE include matrix metalloproteinase-9 (MMP-9) and plasma activator inhibitor 1 (PAI-1). CSF levels of interleukin 6 (IL-6) and interleukin 8 (IL-8) are significantly correlated with MMP-9. Aside from BBB, other brain structures which are disrupted enhancing the penetration of the central nervous system (CNS) include the meningeal barrier, and the choroid plexus. Aseptic meningitis occurs as a result of a breached meningeal barrier in SLE patients and also with non-steroidal anti-inflammatory drug (NSAID) use. Similarly, due to immunosuppression, infectious meningitis is likely. Studies involving the choroid plexus have shown that in SLE patients, immune complex deposition is evident but nonspecific [4, 5].

The most recent studies have referred to the proposed two pathologic mechanisms contributing to the development of NPSLE, the autoimmune or inflammatory pathway and the ischemic or thrombotic pathway. The previous pathway includes autoantibodies, proinflammatory cytokines, chemokines, microglia and C1q while the latter involves the immune complexes, complement system and the aPL autoantibodies. Both of which manifest with focal and diffuse neuropsychiatric symptoms [6].

Intrathecal IgG production is found elevated during a central nervous system flare. The aPL antibodies are directly related to focal NPSLE via autoantibody-mediated thrombosis. This predisposes aPL-antibody positive patients for the increased risk of cerebrovascular events such as stroke and transient ischemic attack (TIA). Studies also shown that aPL antibodies hasten the process of atherosclerosis among susceptible individuals. The risk of developing NPSLE is twice as likely among those with aPL antibodies than those who are aPL-antibody negative individuals. Seizures, chorea, cognitive dysfunction and myelopathy were also observed among those with aPL antibodies. On the other hand, greater cognitive impairment manifests with persistently elevated anti-cardiolipin. This consistent finding is also similar among SLE patients

Intrathecal	IgG
	PAI-1
	MMP-9
Antibodies	aPL
	anti-ribosomal P
	AECAs
	anti-MAP2
	anti-AQP4
	anti-NMDAR/NR-2
	anti-suprabasin
CSF	IL-6
	IL-8
	IL-2, IL-10

PAI-1: plasma activator inhibitor; MMP-9: matrix metalloproteinase; aPL: antiphospholipid; AECAs: anti-endothelial cell autoantibodies; anti-MAP2: anti-microtubule protein 2; anti-AQP4: anti-aquaporin 4; anti-NMDAR/NR2: glutamate receptor antibodies; and IL: interleukins.

Table 1.
Antibodies/proteins of interest implicated in NPSLE.

with positive lupus anticoagulant. The ischemic events are implicated in the brain regions including the amygdala, frontal cortex and hippocampus. The anti-ribosomal P antibodies have not been associated in coexisting cognitive impairment. These antibodies have an association with NPSLE, particularly psychosis, but are not reliable to make a diagnosis. These are highly specific for SLE and found to be present in up to 46% of patients with SLE. Other NPSLE syndromes including seizure, coma, depression, aseptic meningitis and transverse myelopathy are also associated with these antibodies. MAP-2, a cellular protein, is strictly found in neurons and essential to the cytoskeletal integrity. In one study, involving 100 SLE patients and 74 patients with various neurologic disorders, it was found out that more SLE patients as compared to neurologic disease control patients have presence of anti-MAP-2 antibodies (17% vs. 4%, $p = 0.028$) AQP4 is a water channel protein expressed on astrocytic foot processes around blood vessels controlling the flow of water into and out of the brain. In one study, anti-AQP4 antibodies were detected in 3% of all patients with NPSLE and 27% of patients with NPSLE who had demyelinating lesions. Suprabasin is a protein used as an epidermal differentiation marker. In one study it was found out that titers of anti-suprabasin antibodies were higher in the patients with NPSLE than patients with non-neuropsychiatric SLE, multiple sclerosis and normal-pressure hydrocephalus. MMP-9 enhances T cell migration through connective tissue. It is secreted by cells found in the walls of the vasculature including macrophages, T lymphocytes, endothelial cells, and smooth muscle. Intrathecal levels of MMP-9 in significant amount are found in all patients with SLE as compared to non-SLE patients including those with NPSLE. Similarly, intrathecal levels of PAI-1 have been found to be significantly elevated in patients with NPSLE [1, 4, 5].

AECAs play a role in the pathogenesis of NPSLE. It recognizes molecules bound to endothelial cells, antigens expressed constitutively or cytokine-induced and adhesion molecules. Psychosis and depression are also implicated with AECAs due to vasculitis

via expression of adhesion molecules, cytotoxic effect, induction of apoptosis and the activation of coagulation cascade [7].

Previous studies have revealed the associations of elevated CSF IL-6 levels with seizures and IFN-α with lupus psychosis. Some evidence suggested the roles of other cytokines including IL-2, IL-8 and IL-10. Another interesting study involves microglial cells. They play a fundamental role in regulating BBB function and in shaping brain circuits and development ('synaptic pruning') [8].

3. Clinical manifestations

The American College of Rheumatology (ACR) subcommittee categorized NPSLE into 19 distinct syndromes encompassing the CNS and PNS. CNS manifestations include acute confusional state, psychosis, headache, and mood disorders for the diffuse processes (**Table 2**). On the other hand, seizures, myelopathy and chorea are the CNS focal manifestations [1].

In a meta-analysis of 5057 SLE patients, it was found out that NPSLE prevalence varied from 17.6 to 44.5% in retrospective and prospective studies [8]. NPSLE may be the first manifestation of the disease. CNS syndromes are more common than peripheral [9]. The most frequent NPSLE manifestations are headaches, depression, anxiety and cognitive dysfunction. In one study, ethnicity and older age are factors associated with earlier neuropsychiatric damage [10].

Headaches manifest in more than 50% of SLE patients with both migrainous and tension-type headaches being described [1]. Headache in SLE is not associated with disease activity, treatment, imaging such as MRI and biomarkers including aPL, anti-P, and glutamate receptor antibodies (anti-NR2) or any specific antibody. Seizures occur in about 10 to 20% of SLE patients and associated with increased morbidity and mortality. Generalized tonic-clonic seizure is the most common type. In contrast to headache, seizure tend to be associated with APS, disease activity, severe organ damage and other NPSLE manifestations. It is crucial to rule out other causes of seizures such as infections [9, 10].

Cognitive dysfunction which manifests with deficits in memory, thinking and concentration is increasingly observed among SLE patients. Studies suggested the association of aPL, anti-NMDAR/anti-NR2 antibodies, and anti-Sm antibodies [1, 9].

Psychosis, depression and anxiety can occur in SLE. Postal et al. found that mood disorders were associated with disease activity, high prednisone doses, cutaneous disease, and longitudinal extensive transverse myelitis [11]. Depression is the most common disorder in NPSLE, and its lifetime prevalence may reach 65% [12]. Higher incidence of depression among SLE patients were associated with anti-P and anti-NMDA receptor autoantibodies [9]. Interestingly, anti-P antibody levels were 5- to 30-fold higher during the active phase of SLE psychosis, but not during other SLE manifestations [13]. Also, it is very important to consider the differential diagnoses of psychosis in SLE patients such as CNS infection, primary schizophrenia, metabolic abnormalities and psychosis secondary to glucocorticoid therapy or illicit drugs [1]. Anxiety disorders are common and found in up to 40% of SLE patients [14].

SLE patients are susceptible to developing cerebrovascular events such as ischemic stroke and intracerebral hemorrhage with the previous more common than the latter. The development of cerebrovascular disease in SLE patients can be attributed to accelerated atherosclerosis and inflammatory mediators such as cytokines, aPL antibodies and complement system [1, 9]. In relation to which, one systematic review

PNS	CNS
Autonomic Disorder	Aseptic meningitis
Cranial neuropathy	Acute confusional state
Guillain-Barre syndrome	Anxiety Disorder
Mononeuropathy, single/multiplex	Cognitive Dysfunction
Myasthenia gravis	Cerebrovascular Disease
Plexopathy	Demyelinating syndrome
Polyneuropathy	Headache
	Mood Disorder
	Movement Disorder
	Myelopathy
	Psychosis
	Seizure

PNS: peripheral nervous system; and CNS: central nervous system.

Table 2.
American college of rheumatology classification of neuropsychiatric syndromes in systemic lupus erythematosus.

found a fivefold increase in the risk of ischemic stroke in patients with aPL antibodies compared to controls [15]. Posterior reversible encephalopathy syndrome (PRES) is a known mimic of CNS lupus. It is characterized by headache, seizures, altered consciousness, and visual changes often in a background of hypertension, eclampsia, renal disease and/or immunosuppressive therapies [1].

Chorea is the most common movement disorder observed among SLE patients. It appears in 2–3% of adult patients more common in women. Recent evidence suggests an autoimmune mechanism related to aPL antibodies. Aseptic meningitis is also a manifestation of SLE. It can occur at any time during the disease course presenting with headache and/or altered mental status. Other causes include infections of various etiologies (bacterial, viral, fungal or tuberculosis), immunosuppressants or medications and malignancy [9, 10].

Optic neuropathy and myelopathy rarely occur as part of the spectrum of NPSLE. The manifestations of optic neuropathy include monocular central visual loss, color vision and afferent pupillary problems. It can be caused by thrombotic or inflammatory mechanisms in the setting of lupus. On the other hand, myelopathy is a syndrome affecting the spinal cord presenting with numbness, paresthesia of bilateral lower extremity and weakness that can progress to involve the upper limbs. A characteristic symptom of which is a band-like pain or discomfort around the abdomen [1]. Lupus myelitis occurs in about 1.5% of cases. In nearly half of the patients with SLE, acute transverse myelitis occurs as the first clinical manifestation within the first 5 years of diagnosis. Histopathology findings revealed ischemic or thrombotic myelopathy or a localized inflammation [9]. Several studies link transverse myelitis-SLE with aPL antibodies [16].

Demyelination in NPSLE is also seen in about 0.3% of cases. It can be an isolated syndrome but can overlap with multiple sclerosis [17]. SLE patients also present with peripheral neuropathy. One study had demonstrated a 6% prevalence of peripheral neuropathy, 67% of which were attributable to SLE. Sensorimotor axonal polyneuropathy was the most common type. Similarly, it is crucial to rule out other causes of

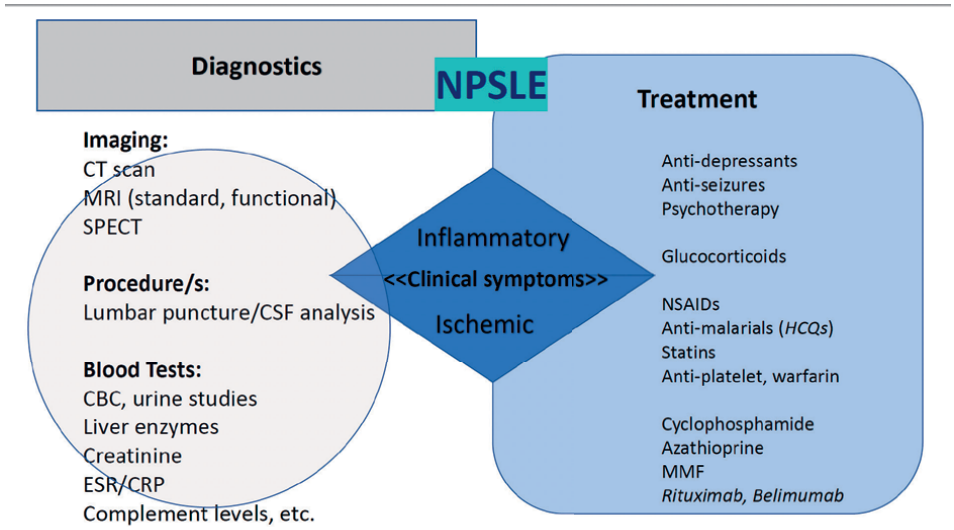
peripheral neuropathy such as diabetes mellitus, hypothyroidism,, infections, vitamin deficiency, malignancy and drugs [1].

4. Diagnosis

The approach to diagnosis of NPSLE remains challenging as clinicians need to be thorough when it comes to history taking, physical examination and other methodologies including serologic examination, imaging and medical procedures (e.g. lumbar puncture) that can facilitate accurate diagnosis. Primarily, the arduous task begins with identifying whether the manifestations are secondary to the disease activity or not. These steps and processes will help in identifying the pathogenetic pathway involved and the proper course of management at the end (**Figure 1**).

Based on the presentation of the neuropsychiatric signs and symptoms, the assessment process should be tailored-fit accordingly. Likewise, localizing the areas of the CNS involved also has its limitations. In example, the focal neurologic symptoms correlate well with the conventional magnetic resonance imaging (MRI) but abnormalities associated with altered perfusion or neurometabolite changes can be best demonstrated by functional imaging techniques [4]. However, more than half of patients diagnosed with NPSLE have a normal MRI of the brain [18]. Single photon emission computed tomography (SPECT) provides an estimate of regional cerebral blood flow and thought to be more sensitive than MRI for the evaluation of NPSLE. But studies were inconsistent [19].

Computerized tomography (CT) is being used to exclude focal abnormalities such as hemorrhage, infarcts, tumors, cortical atrophy and calcifications. On the other hand, metabolic neuroimaging such as positron emission tomography/PET,



NPSLE in summary featuring the basic diagnostic approach and management.

Figure 1.
NPSLE in kaleidoscope. NPSLE in summary featuring the basic diagnostic approach and management.

MR spectroscopy) and perfusion imaging such as single photon emission computer tomography/SPECT) can detect abnormalities in patients with psychiatric manifestations but otherwise have normal MRI studies [4]. Functional MRI (fMRI) also is being used to assess for cognitive function in SLE.

CSF analysis is utilized in cases of ruling-out infection. Likewise, it becomes as important in some cases such as aseptic meningitis, transverse myelitis and vasculitis.

Biomarkers are also used to better screen and monitor treatment for NPSLE. At present, the autoantibodies used in the diagnosis and therapeutic decisions include antineuronal, anti-ribosomal P, and anti-NR2 antibodies. Meanwhile, other than autoantibodies, chemokines and cytokines, intra-thecal levels of PAI-1 and MMP-9 are used for screening & monitoring purposes.

Magro-Checa et al. proposed a diagnostic approach based on the clinical presentation of patients with NPSLE manifestations. This consisted of matched diagnosis and work-up, procedure or imaging to be done. On the other hand, there have been attribution models proposed in order to strengthen the diagnosis. These were developed very carefully and limitations were also determined accordingly [17].

In an international inception cohort study Hanly et al. described an attribution model in which the level of stringency was based on three simple rules that take into account the temporal relationship between the neuropsychiatric (NP) event and the diagnosis of SLE, the type of NP event and a comprehensive list of exclusions or associations according to the American College of Rheumatology (ACR) nomenclature. In this study, they concluded that 28% of SLE patients experienced at least 1 NP event around the time of diagnosis of SLE, of which only a minority were attributed to SLE [20].

Bortoluzzi et al. developed a new algorithm for attribution of neuropsychiatric events in SLE in 2015. This enabled identification of which NP events have a high probability of being or not being attributed to the disease among SLE patients in a more standardized and reproducible manner. When compared with expert clinical judgment, it demonstrated a good performance in sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) with a confident assumption of correctness at 33%. However, this was not intended as a substitute for clinical judgment which remains as the cornerstone of the diagnosis and management of NPSLE [21].

Magro-Checa et al. in 2017 provided a prospective date from the Leiden NPSLE cohort and determined the value of multidisciplinary reassessment in attribution of neuropsychiatric events to SLE. This model has showed that each NP event was attributed to one of the following groups: NPSLE or NP events directly related to SLE, undefined NPSLE, and non-NPSLE or NP events better explained by other etiology. Non-NSPLE events were divided further into subgroups: due to primary NP disease, due to medication or drugs, due to a complication of SLE and due to other concomitant disease. This model showed reassessment of NP symptoms in SLE and re-classified a total of 13.8% of NP events. Furthermore, the percentage of NP events attributed to SLE was 31.3% [22].

Individualizing the approach to each patient presenting with NPSLE is also applicable since there is no gold standard in the approach to diagnosis. The complexity of the signs and symptoms necessitate a diagnostic algorithm applicable for the most number of cases.

5. Treatment

Besides the general treatment which includes control or correction of aggravating factors, nonpharmacological interventions and symptomatic therapy for the different

syndromes associated with NPSLE, the approach also depends on which pathway is primarily involved. Govoni et al. had illustrated the current treatments on NPSLE. In this study, it had been emphasized that the identification of the most likely cause and contributing factors to the NP event is determined by careful assessment and utility of diagnostic tests that are deemed appropriate. Similarly, it is important to determine whether the disease activity is reversible or irreversible by treatment as this can provide the framework for the appropriate modality in each patient [8].

Magro et al. provided a detailed review on the therapeutic strategies in NPSLE from the general treatment to therapies specific for the pathway that is involved (ischemic vs. inflammatory). In this perspective, it is pointed out that a combination of immunosuppressive therapy and secondary prevention may be used in the same patient when both ischemic and inflammatory pathogenic mechanisms are suspected [22].

In clinical practice, therapy will be directed at inflammation or at prevention of ischemic events upon confirmation of the most likely process involved. Psychotherapy had a beneficial effect on anxiety, depression and quality of life in a controlled clinical trial in 80 SLE patients [23]. Positive outcome with antidepressants had been reported in some observational studies [24]. The use of antiseizure drugs in SLE has also not been subjected to controlled clinical trials while antipsychotic medications are used in the majority of patients with lupus psychosis [25, 26]. Among medications used for generalized seizures include barbiturates and phenytoin while for partial complex seizures may include clonazepam, valproic acid and carbamazepine. Nonsteroidal anti-inflammatory drugs (NSAIDs) are used for pain relief such as headache [22]. Systematic studies in SLE patients are lacking focusing on behavioral rehabilitation of cognitive dysfunction [8].

The presence of aPL antibodies predisposes to the development of thrombotic events such as stroke and prior ischemic events. Primary prevention in APS does not support the use of low-dose of aspirin or warfarin according to current evidence and still necessitates large and well-designed clinical trials [27]. SLE patients with focal manifestations attributed to aPL antibodies requires lifelong anticoagulation [28]. Warfarin is used in the prevention of recurrent thrombosis. Other adjunctive therapies of use are antimalarials including hydroxychloroquine, statins, and antiplatelet agents. Antimalarials exert beneficial effects both as anti-inflammatory and antithrombotic.

In NPSLE patients, the use of glucocorticoids is based on clinical experience. Methylprednisolone pulse therapy consisting of 1 g intravenously for three consecutive days followed by tapering doses of oral prednisolone depending on the severity of NPSLE manifestation is a usual practice. This is acknowledging that the mechanism responsible is inflammatory in nature similar to when other organ systems are affected during lupus flares. Positive effects of cyclophosphamide treatment had been described in several case series [29, 30]. One retrospective study involving 31 NPSLE patients suggested benefit from glucocorticoid use and monthly intravenous cyclophosphamide (250–1000 mg/m^2) [31]. Furthermore, Stojanovich et al. concluded in a study involving 60 NPSLE patients that patients treated with cyclophosphamide showed more clinical and eletrophysiological improvement on cerebral function [32].

Due to mild side effects, azathioprine is frequently used for maintenance therapy or as a steroid-sparing agent. There are very few data on the effects of azathioprine in NPSLE. In a study by Ginzler et al. including 68 SLE patients with poor prognosis due to renal or NP events, 54 patients treated with azathioprine had improved significantly on long-term survival and fewer hospitalization. In clinical practice, similar

with previous medications, although not yet supported by current evidence, azathioprine is widely used as maintenance therapy after cyclophosphamide in patients with severe NSPLE manifestations and even as an option in mild NPSLE [33].

The effect of mycophenolate mofetil in NPSLE patients is described in very few cases and not conclusive. Similarly, the use of methotrexate is very rarely use in NPSLE and evidence is limited to several case series via intrathecal route. Meanwhile, the efficacy of plasma exchange or cyclosporin A remains unknown because of concomitant use [34].

The effect of biologic therapies remains limited including rituximab, belimumab, and anifrolumab. The use of rituximab alone or in combination with other immunosuppressives like cyclophosphamide have reported positive effects but needed more studies [35–37].

6. Conclusion

NPSLE remains an area of great interest focusing further on the pathogenetic mechanisms, approach to diagnosis and treatment. There have been a lot of limitations described in the previous studies including the lack of well controlled clinical trials, biomarkers and novel therapies. These are the challenges in which current and future researches revolve for the benefit of SLE patients.

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Section 5

Fertility and Lupus

Chapter 9

Fertility, Pregnancy, and Systemic Lupus Erythematosus

Marcela Catalina Fandiño Vargas

Abstract

The desire for pregnancy in patients with systemic lupus erythematosus (SLE), which was previously considered a potentially lethal enemy for the mother and the product, today is part of the success of advances in the treatment and control of the disease. In this chapter, we will talk a little about the pathophysiology of the pregnancy of the patient with lupus, going through the relationship with the treatments received, and the way in which these can directly affect fertility and pregnancy. We will also briefly comment on the compromise of the product in the case of neonatal lupus, and if it really has to do indirectly or directly with the existence of SLE in the mother. We will address pregnancy-related complications along with biomarkers and clinical signs that could indicate inherent risks already widely known in the literature.

Keywords: lupus nephritis, contraception, neonatal lupus, abortion, antiphospholipid syndrome, relapse, hydroxychloroquine, preeclampsia, hypertensive disorders of pregnancy, proteinuria

1. Introduction

Talking about lupus without talking about the reproductive probability of women is impossible. They go hand in hand, first because the disease is more common in patients of childbearing age, and because in the past pregnancy was an absolute contraindication. In current time a normal pregnancy we can achieve it as possible and also its activity since it plays an important role in the occurrence of relapses and therefore complications that generate morbidity and mortality in both mother and fetus. In this chapter, we are going to talk about a "deck" of possibilities of existing complications in the mother, also something about anti-inflammatory drugs and their use in pregnant patients and superficially direct effects of the disease on the product.

Currently, all processes related to reproductive health, such as contraception and stricter control of pregnancy, are more frequent for patients with good results in most cases, but without neglecting the fact that pregnancy continues to be associated with greater maternal morbidity and mortality and fetal. When reviewing the literature and in daily practice, we find that the persistence of activity in pregnancy has been directly related to estrogen levels. This "time bomb" triggers maternal, pregnancy-related, and fetal complications. In the case of the mothers, lupus outbreaks, with important compromises in target organs (brain, kidney, vascular, placenta, and

lung). Obstetric complications (fetal loss, intrauterine growth retardation, and premature birth) and their incidence increase when it is related to anti-phospholipid antibody syndrome and in the newborn indirectly cases of neonatal lupus due to the transplacental passage of antiantibodies [anti-Sjogren's syndrome A (SSA) or anti-Sjogren's syndrome B (SSB)] [1]. Unquestionably, for a good outcome and development of these pregnancies, preconception counseling must be strictly followed, plus multidisciplinary management by a rheumatologist, gynecologist or perinatologist, nutritionist, and psychologist. The primary objective to achieve success in pregnancy and the reduction of complications is mainly that there is no lupus activity in at least 6 months, with an adequate prescription of medications that are safe in pregnancy, always taking into account clearly the patients and their risk factors, and mandatory regular follow-up [2].

2. Before the beginning

2.1 When you don't know, it's no!!

This point of the chapter is essential given that a large number, not to mention all, of the patients with systemic lupus erythematosus (SLE) are of childbearing age and previously aware of the hormonal effect on which the disease is active. It is very important that the type of treatment received by the patients is also taken into account since several medications have a teratogenic component [1].

2.1.1 There is desire we don't know it's

Patients with SLE should, as far as possible (and in an ideal world of course), receive clear, precise and, above all, timely advice on contraception, the effect of the medication on the product, and its suspension in the event of an unplanned pregnancy. And why not say it, the possible outcomes in the absence of strict control and clear communication in the relationship between the doctor and the patient, to reduce complications, answer questions, and clear up any doubts that arise at the time. This must always go hand in hand individually with each of the patients since each one of them is a "world apart." Always taking into account the risk of each one not only due to the existing disease but also due to others that add up to further complicate the picture [3]. With this we can address, apart from SLE, chronic degenerative diseases together, such as high blood pressure, obesity, smoking, and in some other patients ask about existing family history of cancer that is hormone dependent. Together with SLE, the association with antiphospholipid antibody syndrome (APL) must be sought insistently, since this leads to an increased thrombotic risk.

The planning of the pregnancy by the multidisciplinary medical team and the patient increases the probability of a successful outcome and is a vital strategy to reduce perinatal morbidity and mortality complications, recognize them if they occur and make an "itinerary" with stations in which the patient knows how to deal with each of them always hand in hand with the medical team [4]. When preconception counseling begins, the main complications that could arise in pregnancy should be explained in detail, slowly and with the greatest simplicity, but without losing the meaning of the counseling.

2.1.2 Contraceptives: when you already know what you want but you cannot and you want to avoid it!

In the twenty-first century and despite advances in technology and communications, there are still problems with advising patients with SLE regarding contraception [4]. It is a vital part of the strategy to control the decrease in perinatal morbidity and mortality that women with SLE can access information on contraceptive methods and always according to the activity of the disease and the risk factors that each one of them has individually. Despite of that can increase in a prospective observational study of 86 patients, 59% had no advice regarding contraception despite using highly teratogenic drugs, 22% used contraceptives, and 53% only used barrier methods [5].

Looking at the existing literature and evidence, it could be said that we are slowly finding "clarity in a world of greys." On the one hand, it was shown in a case–control study that there is a higher risk of developing disease activity in women aged 18–45 years who are using contraceptives based on combinations of estrogens or progestins with high doses of ethinylestradiol and that the time of starting the intake is recent [6]. On the other side of the coin, we find two randomized controlled trials that showed that the combination of estrogen and progestin or progestin alone does not increase the incidence of thrombotic events in patients as long as they have low or no disease activity and that there is no previous history of thrombosis and negative aPL titers [7]. On the contrary, in patients who are positive with high titers of antiphospholipid antibodies (whether or not they have antiphospholipid syndrome) added to risk factors for developing thrombotic events in which contraception with estrogen-based preparations (oral pill, vaginal ring, and patch transdermal) is contraindicated. In young women with a history of coronary thrombosis (myocardial infarction), cerebral thrombosis (ischemic stroke), and who have a positive lupus anticoagulant, the use of the combined pill increased the risk of thrombotic events at the arterial level [8].

However, in patients who are on strict anticoagulation and who generally have a low-risk antiphospholipid profile, progestogen alone (pill, depot subcutaneous injections) could be considered, provided there was no history or no high risk of thrombosis. Intrauterine devices (IUDs), such as the copper one, can be used in any patient with SLE relatively safely [1, 3]. The levonorgestrel-containing IUD could be used as long as the risks vs. benefits are weighed, and this by reviewing each patient individually. For emergency contraception, the progestogen combination is not contraindicated.

3. In the beginning

God blessed them and said to them, "Be fruitful and increase in number; fill the earth and subdue it."
Genesis 1:28.

3.1 The delicate hormonal axis in women and the relationship with autoimmunity: when despite the intention something is not right!

Sex hormones are actors of great importance for the maintenance of the existing balance in the immune system. These hormones (estrogens and progesterone) and

with them prolactin have many effects on cellular and humoral immunity and on various processes together. Clinical experience has shown that some changes in this delicate hormonal balance can contribute to a greater or lesser activity of SLE, such as the use of exogenous estrogens (oral contraceptives or postmenopausal hormone therapy), and hormonal changes where there is an increased secretion of endogenous estrogens such as those associated with pregnancy.

In reproductive pshysiology that leads to the successful implantation of the embryo, with the necessary protection against immune rejection due to being a semi-allograft and at the same time maintaining close control of the immune system and adequate response of the same during pregnancy and childbirth [9]. To achieve this goal, an arsenal of inflammatory mediators is needed, and for this reason, it is logical that many of the inflammatory or immune responses have the female sex steroids as protagonists: estrogen, progesterone, and prolactin (**Figure 1**).

It has been found that there are estrogen receptors (α and β) that are essential for estrogen to act, and antibodies against these receptors, especially anti-Erα, have been detected in patients with SLE. These caused the induction of cell activation and apoptosis in lymphocytes and are closely related to the induction and maintenance of T-cell anergy and immune self-tolerance [10, 11].

One study analyzed the presence of specific antibodies against estrogens in patients with SLE. It was observed that in 45% of the patients studied these antibodies were found and induced cell activation and subsequent apoptosis in lymphocytes. There is a theory of the existence of an extracellular binding domain where these antibodies enter the cell and associate in some unknown way with the cell membrane, initiating the activation of the ERK/MAPK pathway when this is very important for selection, differentiation, and maturation of T cells and modulates their induction, their anergic quality, and self-tolerance. These antibodies could induce cell apoptosis and repeatedly alter cell-cycle control and modulation in T lymphocytes [12].

3.2 Pregnancy immunology: when the miracle has already taken place!

Progesterone is essential for the initiation and maintenance of pregnancy as it has important effects on the immune system [13]. These effects are coordinated by a progesterone-induced blocking factor (PIBF). This is encoded in a target gene located on chromosome 13 in humans. This protein has some isoforms, which act as cytokines, that exert their action on the metabolism of arachidonic acid, inhibit arachidonic acid by the direct action of phospholipase A2 and the subsequent decrease in prostaglandin and/or leukotriene synthesis.

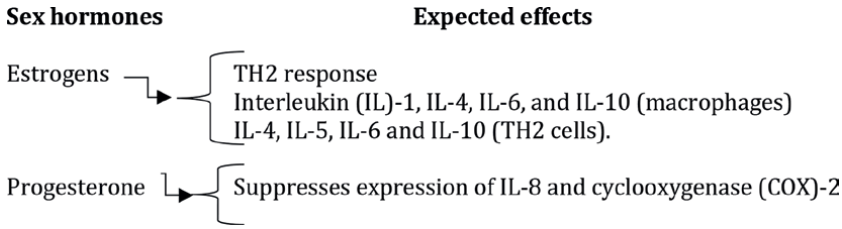

Figure 1.
Expected effects of sex hormones on the immune response.

Full-length PIBF (90 kDa) is anchored in the nucleus and is involved in cell-cycle regulation. The expression of PIBF seems to be crucial for the normal progression of pregnancy, which is why it is found in the lymphocytes of pregnant women as well as in other tissues inherent to pregnancy and has also been found to be related to the proliferation of cancer cells in tumors malignant [14]. The decreased production of this factor results in an alteration of the cell cycle with the consequent deregulated and uncontrolled invasion of the trophoblast, if it is the isoforms that are absent, it could result in the loss of local immunosuppression, necessary for maintenance and vitality of gestation.

NK (natural killer) cells tend to differentiate during pregnancy. While ordinarily, 90% of peripheral NK cells express a low density of CD56dim molecules and high levels of CD16; most decidual NK cells express a high density of CD56bright and not CD16. These secrete angiogenic factors and cytokines, and one of their functions is to control placentation in an orderly and adequate manner [15]. Peripheral CD56dim NK cells are cytotoxic, whereas CD56bright are not. The job of PIBF is to inhibit the release of perforins from activated peripheral NK cells and this, in turn, helps to maintain the low level of lytic activity of decidual NK cells.

It is understood that during pregnancy there is a predominantly Th2 immune response; however, there are certain moments of it where there is a change in response, for example at the time of implantation or at the time of childbirth.

Evidently, progesterone and PIBF alter cytokine homeostasis in favor of a Th2 response. And so, a nonhostile immune environment is promoted by the increase in IL-10 and regulatory T cells [16]. This response slowly changes and gradually reverses before the onset of labor. Progesterone reduces proinflammatory and cytotoxic T-cell responses by effectively modulating immune cell-mediated interactions and regulating differentiated memory cells. In a normal gestation process, PIBF in urine and serum increases until the 37th week of gestation, followed by a sharp decrease in labor. Whereas, in a pathological pregnancy, the levels of PIBF in urine do not increase. The onset of labor (both term and preterm) is predictable based on PIBF levels [17].

3.3 Immunology of pregnancy: the dance of the mother/fetus binomial

1. Recognition of fetal antigens: this recognition is carried out by Vγl cells (subset of γδT cells) that are found in greater proportion in the decidua.

2. Upregulation of progesterone receptors: these Vγl (CD56+) cells become activated and develop progesterone receptors.

3. Production and release of PIBF: when there is a conjunction between progesterone, CD56+, and 76+ cells, decidual NK cells together with a positive progesterone receptor carry out the synthesis of PIBF.

4. Pregnancy protection: this release of PIBF contributes to the success of the pregnancy through three actions: it induces an increase in "blocking" antibodies, Th-2 dominated cytoprotective immune response, and a reduction in NK cell activity. This will prevent the possibility of presenting inflammatory and thrombotic diseases in pregnancy (**Figure 2**) [18].

We forget the very important role of the major histocompatibility complex (MHC) that protects the trophoblast from the destruction of the NK by inhibiting its lytic functions, as well as limits the cytotoxic activity of leukocytes, suppresses the

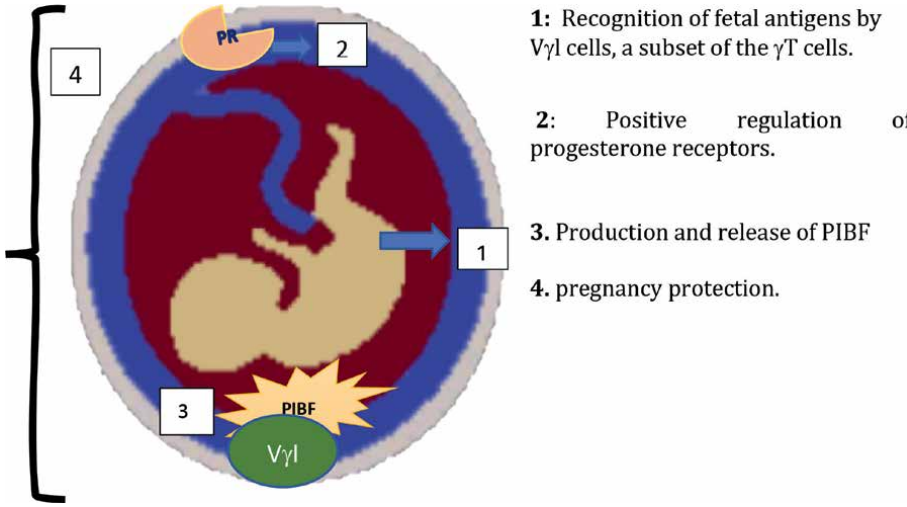

Figure 2.
Sequence of events in the immunology of pregnancy between the mother/fetus binomial.

production of cytokines of type proinflammatory, and also induces T cell apoptosis. [19]. Nonclassical MHC antigens also promote trophoblast proliferation and invasion. Altered expression of nonclassical MHC 501 antigens has been linked to recurrent pregnancy loss and preeclampsia. Placental expression of FAS ligand may also play a role in pregnancy success through the selective removal of antifetal T-cell clones.

3.4 Fetal Immune System

It begins at the moment of conception and continues until birth and later in infancy. In the first weeks of gestation, pluripotent stem cells form all the components of blood cells. In the sixth week, the thymus forms and lymphocyte differentiation begin. Subsequently, the first lymphocyte bud appears along with the plexuses. At the end of the first trimester of pregnancy, the fetus already has the ability to respond, although it decreases infections because there is already production of plasma cells and antibodies.

The trophoblast continues to develop as a barrier that is not entirely infallible but is effective in preventing the passage of cells with immunological capacity. Even thought maternal IgG action of placental Fc receptors passes a barrier levels are barely perceptible at the beginning of pregnancy; they have a slow increase in the second trimester and equal and reach maternal serum concentrations at 26 weeks of gestation reaching its maximum transfer in the last 4 weeks of gestation. Humoral immunity in the neonatal period depends exclusively on circulating immunoglobulins that have crossed the placenta. This is why potentially harmful maternal autoantibodies (anti-SSA, anti-SSB, and anticardiolipin) will pass into the fetal circulation and will have harmful potential just as maternal exposure to IgG-based pharmaceutical agents will also pass into the fetal circulation [20].

4. Pregnancy and lupus: when we have to face troubled waters!

Pregnancy in women with SLE, especially those with significant renal involvement (lupus nephritis), is associated with an increased risk of developing preeclampsia,

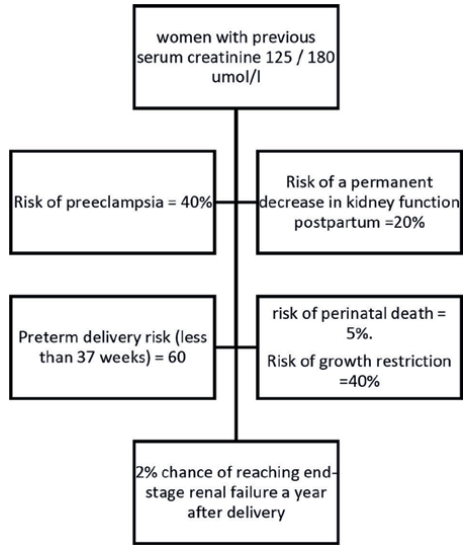

Figure 3.
Consequences of pregnancy in patients with chronic kidney disease and SLE.

fetal growth restriction, fetal loss, and preterm delivery. This risk remains latent, although lupus nephritis is inactive and rises considerably in cases where it is accompanied by proteinuria and/or high blood pressure. If there is already severe kidney damage, the possibility of pregnancy without problems is remote (**Figure 3**) [10].

Lupus activity is a key predictor of pregnancy outcome. High levels of lupus activity before the start of pregnancy increased the risk of pregnancy loss and the risk of preterm delivery up to four times, the latter together with elevated anti-DNAdc (anti-double-stranded DNA antibodies) and low complement [21]. There are other biomarkers that can give clues about poor pregnancy outcomes in patients with SLE: Elevated ferritin as a marker of inflammation and low estradiol as a marker of poor placentation, are associated with preterm birth. In a meta-analysis where 362 patients with SLE were studied, their pregnancies showed an incidence of renal flare from 11% to 43%, acute kidney injury from 3% to 27%, and total loss of renal function in 11%. In another study, 113 pregnancies were evaluated in 81 women with preexisting biopsy with lupus nephritis (six women with class II, eight with class III, 48 with class IV, and 19 with class V). At the beginning of the pregnancy, 49% were in complete remission and 27% were in partial remission. Results included nine spontaneous abortions, one stillbirth, and five neonatal deaths. Thirty percent were premature births, and 33% were babies with low birth weight <2500 g. These outcomes were directly related to hypocomplementemia present at the time of conception and the use of aspirin during pregnancy [22].

Regarding kidney involvement, 33% had kidney flares (both during pregnancy and postpartum), 20 of these patients with reversible symptoms, and three with a progressive deterioration of glomerular filtration. One ended up on dialysis. These results were related to the maternal renal status prior to pregnancy.

In another study, they compared the results of pregnancy in patients with SLE who had already achieved clinical remission, taking into account the DORIS scale (definition of remission in SLE) and LLDAS (definition and initial validation of a lupus low disease activity state). A total of 49 patients were evaluated, when they were

in modified clinical remission and 57 in modified LLDAS. In both groups, outcomes were similar: successful pregnancy, full-term births, fetal loss, miscarriage, small-for-gestational-age infants, low-birth-weight infants, maternal complications, and flares [23].

Pharmacological therapy is another point that must be taken into account due to the potential teratogenic effect of some medications. In general, the therapy used in pregnant women with SLE is safe (prednisolone, azathioprine, and hydroxychloroquine [HCQ]), and can even be continued without problems during lactation. However, in the case of women with lupus nephritis, many receive immunosuppressants such as mycophenolate mofetil (MMF), this drug has teratogenic potential (microtia and atresia of the external auditory canal, orofacial and cardiovascular malformations and digital hypoplasia), for which it should be discontinued before at least 6 weeks before conception in order not to have residual effects due to its enterohepatic circulation [24]. For these patients, the ideal would be to switch to azathioprine. In a study of 23 women with lupus nephritis with a low SLEDAI (Systemic Lupus Erythematosus Disease Activity Index) had switched to azathioprine before conception, there were no flares in 18 pregnancies and only one case in the postpartum period after 17 live births. It was also found that as the dose of prednisolone or SLEDAI was required to be increased, the prognosis of pregnancy worsened [25].

4.1 Preeclampsia or lupus outbreak: "the great simulator":

For several decades and until reactively recently, pregnancy in patients with SLE was discouraged due to the state of maximum activity with which it's related and deleterious consequences. It was routinely considered an absolute contraindication in these women. At present, according to the evidence, we know that it is possible to have a pregnancy with excellent outcomes as long as certain conditions are met (stable SLE or low activity in the 6 months prior to conception, since patients with active disease at this time have the highest risk of an outbreak during pregnancy), and that this is of strict multidisciplinary management. The PROMISSE study (Predictors of Pregnancy Outcome in SLE and antiphospholipid syndrome) determined the degree of risk of exacerbation in women with stable SLE and found that 385 women with SLE (31% with renal involvement/nephritis), the mild or moderate outbreaks reached 15%, while severe ones were 5%. Quite the opposite with patients who became pregnant with the active disease even 6 months earlier, where relapses reached almost 60% [26].

In a prospective study where the outcomes in the pregnancies of 132 women with SLE were studied, there were outbreaks of SLE in 75 of the 132 pregnancies, mild in 84 cases, moderate in 11, and severe in 19. Before pregnancy, 36% had glomerulonephritis, 33% had joint manifestations, 37% had comp hematological disease, 13% had a skin disease, 6% had neuropsychiatric manifestations, and 1% had serositis. During the 6 months before conception, 48% had mild and/or stable clinical manifestations. Anti-dsDNA antibodies were positive in 56% and anti-ENA antibodies in 47%: anti-Ro/SSA: 32.5%, anti-La/SSB: 1.5%, anti-U1RNP: 4.5% and anti-Sm: 6.8%. In the multivariate analysis, the indisputable predictor of relapse of any severity was the number of relapses that the patients had before pregnancy. In each of the groups of outbreaks, according to their severity, there were several predictors that warned about it: mild was associated with hematological abnormalities before pregnancy, moderate was due to low C3 or C4, and severe was due to having involved with renal compromise, some type of glomerulonephritis, before or

during conception. Protective factors it was observed the longer the duration of the disease there is more possibility. Joint involvement was predicted by anti-dsDNA positivity. Borella et al in made a study about pregnancy and SLE in which there were obtained 110 live births of 132 pregnancies. 81 were term babies and 29 were preterm. There were 22 losses: 14 miscarriages, seven stillbirths, and one volunteer. Fetal loss and small gestational age were associated with preeclampsia. Live births were obtained in 110 of the 132 pregnancies. Eighty-one were term babies and 29 were preterm. There were 22 losses: 14 miscarriages, seven stillbirths, and one volunteer. Fetal loss and small-for-gestational-age fetus were associated with hypertension at conception, miscarriage by a number of steroids taken in the last year before conception, stillbirth by a number of relapses in the last year before conception, premature birth and preeclampsia due to the coexistence of APS together with anti-dsDNA antibody levels before conception, and premature rupture of membranes due to a high ECLM (European Consensus Lupus Activity Measurement) score 6 months before conception. First births may be associated with a higher risk of exacerbation in SLE pregnancy compared to subsequent pregnancies, and the pattern of prior SLE involvement may be useful in predicting the course of SLE during pregnancy. Flare manifestations during a woman's pregnancy tend to reflect prior organ involvement [22].

In Asian cohort, 153 patients of 240 pregnancies predominantly Malaysia, India and China there were 61.7% of the cases with complications, being the most common prematurity, miscarriage and presence. Use of HCQ with decrease in complications including preeclampsia, prematurity and intrauterine growth restriction (IUGR) [27].

In a cohort in Trinidad, a cross-sectional analysis and analysis of negative outcomes in pregnancies of 122 Afro-Caribbean women with SLE and without SLE was performed. In women with more that one pregnancy the total number of pregnancies as similar in women with or without diagnosis of SLE. A lower proportion of women with SLE had ever been pregnant compared to women without SLE. In multivariate logistic regression analysis, SLE pregnancies were more than twice as likely to end in stillbirth. The odds of early miscarriage and second-trimester miscarriage were higher in pregnancies with SLE than in pregnancies without SLE. Ectopic pregnancy and preterm birth were higher in pregnancies conceived after diagnosis. Evidence of high levels of both IgM and IgG lupus anticoagulant was found among women who reported three or more miscarriages and elevated IgG in cases of ectopic pregnancy [28].

Pregnancy outcomes in SLE patients, the effect of flare, and treatment on pregnancy outcomes were examined in a study conducted in Saudi Arabia. Pregnancies in patients with SLE and active lupus nephritis, with anti-Ro/SSA antibodies, aPL, hypertension, Raynaud's phenomenon, active disease at conception, and SLE exacerbations, were found to be at increased risk of adverse pregnancy outcomes [29] really without much difference with the other existing cohorts.

In Oman, a study found, apart from the complications already mentioned above where they do not differ from the rest, that pregnant patients with SLE and apart from antiphospholipid syndrome develop deep vein thrombosis and pulmonary embolism; therefore, it is a significant predictor of this type of complications (**Tables 1**–**3**) [30].

According to the Hopkins Center for the management of pregnancy in lupus patients, there have always been three major doubts over time, and thanks to the existing evidence we can know at this time. First, if there really is a greater probability that there will be outbreaks during pregnancy and if so, which organs and/or systems will be most affected. Second, if there will be a renal compromise in these pregnancies and the third is if these patients really have a higher risk of presenting

Prematurity
Fetal loss (miscarriage or intrauterine fetal death)
Intrauterine growth restriction
Small-for-gestational-age newborns
Preeclampsia
HELLP syndrome (eclampsia/hemolysis, elevated liver enzymes, low platelets)
Premature rupture of membranes.

Table 1.
Main complications in pregnancy in patients with SLE.

Disease activity at conception or 6–12 months before
Active nephritis during pregnancy or history of lupus nephritis
Severe organ involvement and end-stage damage to target organs

Table 2.
Factors directly proportional to SLE.

Lupus nephritis = preeclampsia. (Both become indistinguishable)
Premature labor: • Directly proportional to its incidence with the activity of the disease • Relationship with the use of treatment during pregnancy (especially glucocorticoids (prednisone 10 mg/day or higher).
Patients with antiphospholipid antibody syndrome (APS) or SLE with positive antiphospholipid (aPL) with a history of pregnancy morbidity and thrombosis, presence of lupus anticoagulant, and triple positivity for aPL antibodies.

Table 3.
Most common and/or expected adverse results.

complications at the obstetric level. Today, we know that the answer is yes to everything. There is definitely a risk that outbreaks are more common during pregnancy, obtaining similar results in the different cohorts existing at the time, which include patients of all kinds of races, ethnicities, socioeconomic strata, associated comorbidities, etc. These factors are determining [31]. For example, in American studies, more than half of the patients are African–American. In this group of patients, the flare rate is much higher than in Caucasian patients and similar to Indian patients. Outbreaks in the renal and hematologic systems increase during pregnancy, whereas the involvement of the musculoskeletal system is less.

The differentiate lupus flare from preeclampsia, we have certain clinical predictors such as decreased complement serum levels, normal blood pressure and good response to prednisone, the latter use of intravenous to compare will worsen preeclampsia, howewer, it is necessary compare and analize the risk vs. benefity. Now there is the possibility of advising patients with lupus that despite having a lupus flare, their pregnancy can continue and at the same time decrease the activity of the disease as long as the rheumatologist, obstetrician, perinatologist, and other

multidisciplinary team are pending the development and outcome of pregnancy. Because the arsenal of medications allowed in pregnancy is limited, in the acute management of a lupus flare that endangers the lives of patients, sometimes it is necessary to choose between fetal and maternal well-being. The beauty of this is that lupus activity can be controled with prednisone, HCQ and azathioprine. For moderate flare-ups, prednisone at 1 m/k is used, for urgent situations such as severe flare ups, pulses of intravenous methylprednisolone 1000 mg/day dose, for 3 days it's effective.

One of the culprits in pregnant women is for lupus outbreaks apart from estrogens, is prolactin. This is associated with increased disease activity [32]. These patients also have a higher rate of complications in terms of morbidity, especially in relation to metabolic disorders (gestational diabetes and hyperglycemia), hypertensive disorders of pregnancy (including preeclampsia), and urinary tract infections. Greater complications during labor have also been shown, they have a higher risk of premature rupture of membranes and require cesarean sections in a greater proportion than healthy women [33]. In addition, women with SLE who develop anti-prolactin antibodies during their pregnancy are less likely to have both maternal and fetal complications compared to those who do not. For this reason, the administration of bromocriptine with the purpose of blocking prolactin is accepted as a way of preventing relapses during pregnancy and, in turn, obtaining a good result for both the mother and the product. It is administered even postpartum as it is related to less use of immunosuppressants and steroids [34].

5. The fetus and fetal complications: "pandora's box"

The negative outcome of pregnancy in patients with SLE is always due to complications due to abortion, premature birth, and neonatal lupus. We know that this incidence has a multifactorial origin.

In the high-risk pregnancy controls of these women, certain protocols emanating from the existing guidelines and, of course, from the evidence must be adhered to, adjusting the frequency of fetal surveillance according to the maternal and/or fetal status [35]. Fetal surveillance is assessed based on biometry and Doppler ultrasound findings of the umbilical and uterine arteries at 20–24 weeks, since it is extremely valuable data for pregnancy disorders associated with the placenta, such as preeclampsia and IUGR, especially the distinction between early and late, since this will help us to adapt at the time of delivery and thus reduce perinatal morbidity and mortality. The mode (vaginal vs. cesarean section) and timing of delivery are influenced by maternal factors (hypertensive disorders and anticoagulation status) as well as fetal conditions during pregnancy [3].

Neonatal lupus syndrome compromises several organs, where skin involvement can be present at birth, or appear between 4 and 6 weeks of age in the form of erythematous, photosensitive, and ring-type lesions. As the first days of birth go by, the concentrations of maternal antibodies decrease, and with this, they are resolved without major problem. We can also find liver involvement that includes liver enzyme profile without clinical expression, mild hepatosplenomegaly, cholestasis and hepatitis, hematological with manifestations such as anemia, neutropenia, thrombocytopenia and, rarely, aplastic anemia. In a small cases, central nervous system involvement such as changes in white matter, calcification of basal ganglia, and hydrocephalia [36].

The case is different in cardiac compromise because despite being able to have evidence of a structurally healthy heart, the damage produced in the conduction system is usually irreversible. Fetal echocardiography is especially indicated in the context of the presence of maternal anti-Ro/SSA or anti-La/SSB antibodies due to the risk of congenital heart block (CHB), which reaches a rate of 16%. The suggestion accepted so far is to perform weekly fetal echocardiograms from week 16, with great reservations because it is still unknown if it is a truly cost-effective measure that is applicable to all women regardless of whether or not they are at risk of the fetal congenital block, in order to perform screening of these patients [37].

CHB is the most severe manifestation of neonatal lupus. Its pathophysiology is well-documented, where the transplacental passage of maternal antibodies (anti-Ro (Ro52) and Anti La) is related to direct damage to the fetal conduction system from approximately 18 to 25 weeks. The prevalence of CHB is 2% of cases in women with detected anti -Ro antibodies and 10-20% of cases with history of a child with previous pathology. Clinical findings are related to arrhythmias and conduction system abnormalities, such as complete atrioventricular blocks, fetal bradycardia and/or congestive heart failure, premature atrial contractions, pericardial effusion, or tricuspid regurgitation [38]. More than half of the children born with this pathology require the urgent insertion of a pacemaker since it is a life-threatening condition. The most accepted theory is that CHB originates from chronic inflammation of the fetal conduction tissue that mainly affects the atrioventricular node. Histology reports have found lymphocytic infiltrates, antibody and complement deposits, calcification, and fibrosis. It is believed that the presence of maternal antibodies goes hand in hand with autoimmune diseases, such as SLE and Sjogren's syndrome, although it also occurs in women who do not apparently have any disease that explains this association in the fetus. The antigenic components of the antibodies have shown the existence of almost 100% of these directed to the RO-52 protein. Ro60 and anti-La antibodies are also related to CHB to a lesser extent. There are other antibodies that also participate, such as antibodies against muscarinic acethylcoline receptor of neonatal heart. Calreticulin has been indicated as an additional serological marker and is closely related to Sjogren's syndrome [39].

Prenatal therapy with fluorinated steroids (FSs) is performed in cases of incomplete heart block, although evidence indicates that its use in many cases did not prevent the progression of the block and the subsequent need for the use of pacemakers (**Figure 4**).

Therapy with FS can be started as long as both fetal (IUGR and oligohydramnios) and maternal side effects (infections, osteoporosis, osteonecrosis, and diabetes) vs. beneficial effects are taken into account. In a French cohort, it was determined that the use of FS was not associated with CHB regression or increased survival, despite evidence showing positive effects on cardiomyopathy, endocardial fibroelastosis, and hydrops fetalis [41].

In the European and American cohorts, no conclusion was found that could direct treatment. The prognosis after pacemaker placement in children is excellent. In another multicenter study, the combination with FS plus immunoglobulin and plasmapheresis was performed, where better results were obtained compared to those treated with corticosteroids alone. However, in another series, encouraging results were not obtained in relation to the efficacy of monotherapy with IVIG or plasmapheresis.

Regarding treatment, a survey was conducted by the organizing committee of the ninth International Conference on Reproduction, Pregnancy, and Rheumatic Diseases.

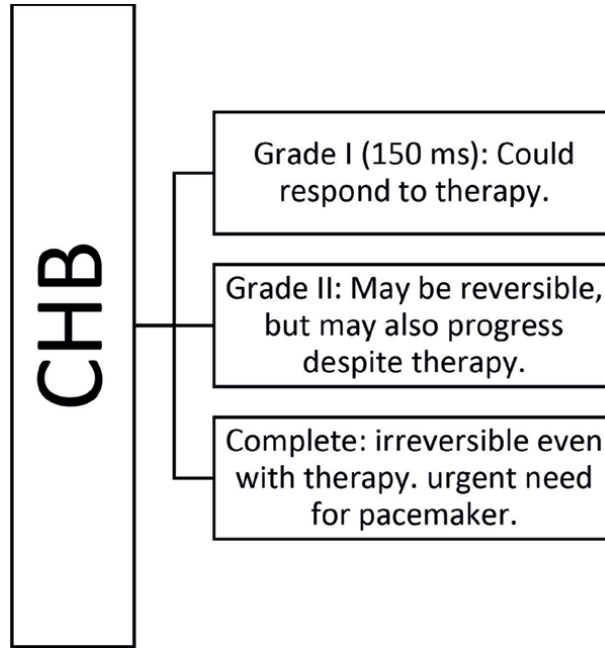

Figure 4.
Response in degrees of blockade to therapy with FSs [40].

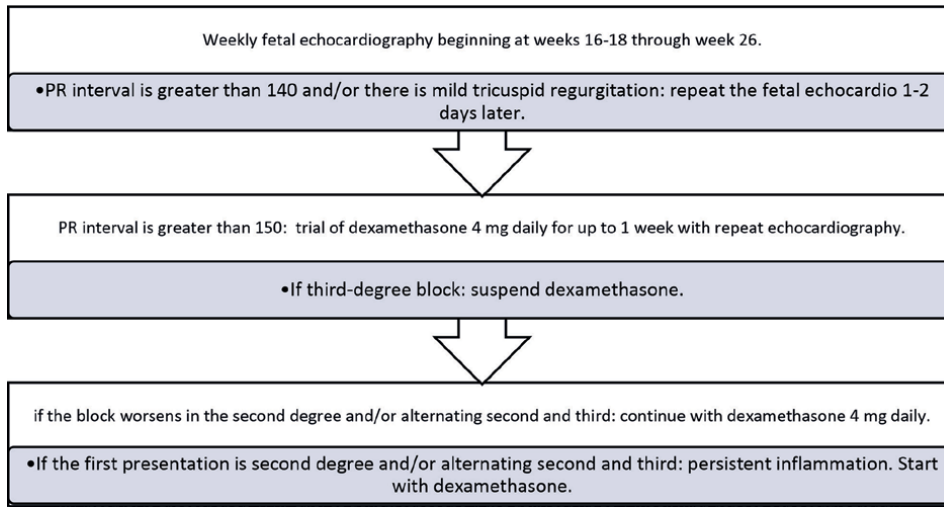

Figure 5.
Buyon scheme for the management of CHB.

For first grade is recommended start treatment with dexamethasone or hydroxychloroquine. For the second degree, dexamethasone was recommended. For third grade, starting dexamethasone or IVIg was recommended, although a percentage (27%) would no longer start treatment. Dr. Jill Buyon, who is an expert on the subject, recommends a treatment scheme according to the weeks of gestation together with the performance of the fetal echocardiogram (**Figure 5**) [42].

Complications associated with neonatal antiphospholipid antibodies: the most frequent are prematurity and IUGR. These patients have a worse pregnancy outcome and neonatal outcome if they already have a history of thrombosis. Antiphospholipid thrombosis is unusual in the newborn or fetus despite the transplacental passage of antibodies.

6. Fertility and assisted reproduction techniques: "when you want to propitiate the miracle despite the risks."

Although there is no evidence that the disease itself decreases fertility, what we do know is that high levels of activity and the use of certain medications can affect the fertility of patients. Cyclophosphamide (CYC), which is the most well-known example of drug, can cause everything from menstrual irregularities to even premature ovarian failure. This will depend on the age of the patients and the dose used and accumulated. When the manifestations of SLE are mild, consideration should be given to not using any treatment that could be gonadotoxic or should be weighed against the risk of ovarian dysfunction. Consider ovarian reserve measures, especially in young patients, if you have important risk factors for a probable alteration of fertility. Usually, the most extensively studied method for the prevention of ovarian failure in patients with SLE includes treatment with gonadotropin-releasing hormone analogs (GnRH-a). This should be administered 22 days before starting or continuing CYC and preferably before starting immunosuppressive treatment.

Embryo and oocyte cryopreservation are options for preserving fertility in patients who are stable enough to safely undergo ovarian hyperstimulation. They are generally safe for patients.

Ovarian hyperstimulation syndrome is a rare complication that results in severe capillary leak syndrome and this increases the risk of thrombosis and renal compromise, which in turn could trigger a flare in patients. However, assisted reproduction techniques have good results and many patients, the vast majority, have been treated prophylactically with anticoagulants. It is imperative to consider prophylactic anticoagulation in patients with high-risk antiphospholipid syndrome and is mandatory for those with confirmed antiphospholipid syndrome. The usual regimen [low-dose aspirin with low-molecular-weight heparin (LMWH)] should be recommended as antithrombotic treatment during pregnancy according to the individual risk profile of each patient.

Concomitant therapy with GnRH analogs, usually leuprolide, appears to decrease the risk of premature ovarian failure. Addressing fertility problems in these patients requires a multidisciplinary collaboration on the part of the perinatologist, obstetrician, rheumatologist, and pediatrician, and this union of powers will make the result favorable and successful [43].

7. Conclusions

- It is duty of physicians to instruct patients with SLE to receive clear, precise and above all timely advice and contraception.

- Pregnancy planning by the multidisciplinary medical team and the patient increases the probability of a successful outcome and is a vital strategy to reduce perinatal morbidity and mortality complications.

- The combination of estrogen and progestin or progestin-only preparations does not increase the incidence of thrombotic events in patients with low or no disease activity, no prior history of thrombosis, and negative aPL titers.

- Patients with contraindication for estrogen-based contraception: who have positivity with high titers of antiphospholipid antibodies (with or without antiphospholipid syndrome) and with risk factors for developing thrombotic events.

- Progesterone is essential for the initiation and maintenance of pregnancy.

- PIBF expression is crucial for normal pregnancy progression.

- Pregnancy in women with SLE, especially those with significant renal involvement (lupus nephritis), is associated with an increased risk of developing preeclampsia, fetal growth restriction, fetal loss, and preterm delivery regardless of activity level.

- CHB is the most severe manifestation of neonatal lupus.

- Prenatal FS therapy in cases of incomplete heart block in many cases did not prevent the progression of the block and subsequent need for pacemaker use.

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Conflict of interest

The author has no conflict of interest for the realization of this chapter.

Nomenclature

SLE	systemic lupus erythematosus
SSA	anti-Sjogren's syndrome A
SSB	anti-Sjogren's syndrome B
APL	antiphospholipid antibody syndrome
IUD	intrauterine devices
ERK	extracellular signal-regulated kinases
MAPK	mitogen-activated protein kinase
PIBF	progesterone-induced blocking factor
NK	natural killer
MHC	major histocompatibility complex
DORIS	definition of remission in SLE

LLDAS	definition and initial validation of a lupus low disease activity state
MMF	mycophenolate mofetil
SLEDAI	systemic lupus erythematosus disease activity index
PROMISSE	predictors of pregnancy outcome in systemic lupus erythematosus
ANTI-ENA	extractable nuclear antigens
ANTI-U1RNP	ribonucleoprotein antibody
ECLM	European Consensus Lupus Activity Measurement
IUGR	intrauterine growth restriction
CHB	congenital heart block
FSs	fluorinated steroids
HCQ	hydroxychloroquine
CYC	cyclophosphamide
GnRH-a	gonadotropin-releasing hormone analogs
LMWH	low-molecular-weight heparin

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